SIXTH ANNUAL REPORT OF THE NATIONAL DIABETES ADVISORY BOARD

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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Public Health Service
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NATIONAL DIABETES ADVISORY BOARD
BETHESDA, MARYLAND 20014

Mailing Address: P.O. Box 30174
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Honorable George Bush
President of the United States Senate
Old Executive Office Building
17th and Pennsylvania Avenue, N.W.
Washington, D.C. 20510

Dear Mr. President:

On behalf of the National Diabetes Advisory Board and pursuant to Public Law 96-538, I am pleased to transmit the Board's sixth annual report. The report presents a concise summary of progress made in the Long-Range Plan to Combat Diabetes and an analysis of opportunities and needs in the future.

Remarkable progress has been achieved in both basic and clinical research as well as in their application to the prevention, diagnosis, and treatment of diabetes and its complications. Adequate Federal support for diabetes at this most opportune time promises to be tremendously cost-effective and would significantly improve the quality of life for millions of our people who bear the burdens of this disease. Unfortunately, the funding of Federal diabetes programs has not kept pace with the opportunities, and measured in inflation-adjusted dollars, it has decreased over the past several years.

The Board is confident that expanded efforts by the Congress and the Administration will hasten progress in the effective treatment and ultimate prevention and cure of this disease.

Respectfully,

James B. Field, M.D.
Chairman, National Diabetes
Advisory Board

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BETHESDA, MARYLAND 20014

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Honorable Thomas P. O'Neill, Jr.
Speaker of the House of Representatives
Rayburn House Office Building
Washington, D.C. 20515

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The Honorable Margaret Heckler
Secretary, Department of Health
and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

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PREFACE

In October 1976, Congress established the National Diabetes Advisory Board to advise Congress and the Secretary of Health and Human Services on the implementation of the Long-Range Plan to Combat Diabetes. The Long-Range Plan was designed to reduce the medical, economic, and social impact of this disease by expanding the national research effort in diabetes and accelerating the beneficial application of cost-effective medical and public health measures.

Previous reports of the Board summarized advances, identified new directions that merited the attention of Congress and the Administration, and recommended priorities for the future. The Board has continued to review progress in the national diabetes program. This sixth annual report presents the Board's latest assessment of the major developments and future opportunities.

In preparing this report, the Board has carefully reviewed progress reports from Federal agencies with responsibility for portions of the Long-Range Plan and consulted with other leaders in areas of diabetes research and treatment.

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1. INTRODUCTION AND RECOMMENDATIONS

Diabetes mellitus is a very serious and costly disease for which no cure has yet been discovered. Although diet, insulin, and other medications are capable of controlling the acute symptoms of the disease, they do not completely restore the normal metabolism of carbohydrate, protein, and fat. The acute and long-term complications of diabetes, which are responsible for the shortened life expectancy and increased morbidity associated with this disease, include an elevated risk of heart and vascular disease, kidney failure, blindness, neurological complications, and adverse outcomes of pregnancy.

Nonetheless, our understanding of the etiology, clinical course, and complications of diabetes mellitus has increased tremendously in recent years as a result of exciting advances in basic and clinical research. At the same time, demonstration programs in selected populations have documented unequivocal reductions in key indicators of diabetes morbidity, including hospitalizations, through the application of currently available prevention and treatment information.

This annual report of the National Diabetes Advisory Board summarizes these and other advances toward the ultimate goal of curing and preventing diabetes and its degenerative complications. The Board's enthusiasm about the accomplishments of the past and our optimism for the future, however, is severely tempered by a concern about the unrealistic budgetary constraints placed upon the Federal agencies responsible for continuing the momentum toward this goal. For example, the percentage of approved high-quality diabetes research projects actually funded by the National Institutes of Health (NIH), the major agency responsible for diabetes-related research, would have declined to an all-time low of approximately 27 percent in fiscal year 1984 if current year budgets for all awards had not been administratively reduced. At the same time, the Centers for Disease Control (CDC), the major agency responsible for disseminating and applying diabetes prevention and control strategies, will have to reduce the level of effort for its diabetes program because the budget has not been increased in 3 years despite inflation.

Advances in science, medicine, and diabetes control offer major opportunities both for reducing the current high rate of complications and for eventually preventing and curing diabetes. It will be a major tragedy, both economic and social, if the current investment in scientific knowledge and control program expertise is not fully exploited to reduce the impact of this disease. Our report, therefore, addresses the financial barriers to future progress.

THE ECONOMIC BURDEN OF DIABETES

Diabetes mortality and morbidity and the associated economic costs are rising due to an increase in the number of people with diabetes and the extended life expectancy of the U.S. population. The annual economic burden of diabetes is at least $10 billion; the social and emotional costs are inestimable. A major portion of the economic burden falls directly on the Federal Government and, ultimately, the taxpayer through the Medicare and Medicaid programs and the direct health care responsibilities of the Veterans Administration (VA), the Indian Health Service (IHS), the Department of Defense (DOD), and other programs of the Public Health Service. The burden of diabetes and its complications also is borne by everyone who pays for health insurance—private citizens, unions, and employers. For example:

- About 25 percent of all cases of end-stage renal failure are now attributable to diabetes. The cost of care for uremic diabetic patients will approach $2 billion a year by the end of this decade. The Medicare-funded End-Stage Renal Disease Program, the Veterans Administration, and the Indian Health Service share the major portion of this economic burden.
- Some 20,000 amputations of toes, feet, and legs are performed annually on people with diabetes. This number represents about half of all nontraumatic amputations in the United States. The hospital costs alone of

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these amputations are about $250 million, more than the total Federal expenditure for all diabetes-related research and control programs. Again, a major share of these expenses are borne by the Medicare/Medicaid program, the Veterans Administration, and the Indian Health Service.

- Diabetes is a leading cause of adult blindness, with about 5,000 new cases occurring each year. Federal and state disability payments, benefits, and rehabilitation services alone total approximately $50 million annually.

ADVANCES IN DIABETES RESEARCH AND CONTROL PROGRAMS

Fortunately, biomedical research has produced tremendously important information in recent years. This information has the potential for significantly reducing the mortality and morbidity and the associated economic burden of diabetes. A few examples are noted here:

- The process for producing human insulin by recombinant DNA technology now assures adequate supplies of this essential hormone.
- The demonstration of immunological and genetic factors in the development of insulin-dependent diabetes has expanded the opportunities to develop preventive therapies.
- Successful islet transplantation across major species barriers in animals has brought this potential cure for insulin-dependent diabetes to the threshold of human application. Segmental pancreatic transplantation has successfully restored carbohydrate metabolism to normal in selected diabetic patients.
- Increasing evidence from animal and human studies indicates that meticulous control of blood glucose has a beneficial effect on the chronic degenerative complications of diabetes.
- The development of insulin pumps now permits the near normalization of blood glucose for prolonged periods of time. Although these devices are not ready for general use, they are facilitating studies to determine whether the complications of diabetes can be reduced, delayed, or prevented by the rigorous control of blood glucose.
- Studies have demonstrated that strict control of blood glucose levels in pregnant diabetic mothers can reduce most of the infant morbidity and mortality associated with diabetic pregnancies.
- Clinical studies have established that laser treatments significantly reduce the risk of blindness from proliferative diabetic retinopathy.
- New pharmacological agents have been developed that may significantly increase our ability to prevent diabetic retinopathy and neuropathy. These agents are being evaluated in collaborative clinical trials.
- Kidney dialysis and transplantation teams in selected centers have demonstrated that the mortality and morbidity rates associated with these procedures in diabetic patients need not differ from the rates in nondiabetic patients.

Although investigators are continuing to seek basic and fundamental information that will eventually lead to the prevention and cure of the disease itself, our ability to treat diabetes and its complications is already increasing. Some of this treatment information is contained in *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners,* recently published by the Board. At the same time, the cost-effective application of current diabetes treatment information is being demonstrated through diabetes control programs sponsored by CDC that integrate current medical knowledge and public health practices. For example:

- A statewide diabetes patient education demonstration program in Maine has documented a net reduction of 32 percent in the number of hospital days required for the 813 participating patients. The savings in hospitalization costs were almost three times the cost of the education program. Similar reductions in hospital admissions were documented following patient education programs in Michigan and Rhode Island.
- Diabetes patient care is being improved in localities encompassed by CDC diabetes control programs. The cost-effectiveness of these interventions has been recognized by many health care organizations and insurance carriers. For example, Blue Cross/Blue Shield, Medicare, and other third-party payors have agreed to reimburse the costs of diabetes outpatient education in some localities after reviewing the findings of these intervention projects. CDC is developing strategies to extend these advances throughout the country.
- The essential components of effective diabetes treatment, education, and control programs have been compiled for use by patients, physicians, and other health care profession-

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als. For example, the aforementioned *Guide for Primary Care Practitioners* presents clinical guidelines directed to the prevention of diabetes-related blindness, amputations, kidney disease, ketoacidosis, and adverse complications of pregnancy. Efforts are under way to disseminate and implement this information.

FISCAL CONSTRAINTS ON MAJOR FEDERAL INITIATIVES

Most of the recent advances in the prevention, treatment, and control of diabetes are a result of increased Federal support during the mid- and late 1970's. However, this impetus has not been maintained in the 1980's. The agencies with the greatest opportunities (NIH, CDC, and IHS) are struggling simply to maintain current programs because available funds have not kept pace with inflation. For example:

- **Biomedical Research—NIH:** Several Institutes at NIH support diabetes-related research. The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), the lead Institute for diabetes research, has historically funded approximately 45 percent of approved scientifically meritorious research applications related to this disease. Estimates for fiscal year 1984 show that this award rate will decline to approximately 33 percent, and would have fallen to 27 percent if the Institute had not decided to reduce the budgets of all previously awarded grants. The Administration's proposed budget for fiscal year 1985 will permit an award rate of only 11 percent unless even deeper cuts are made in all ongoing programs. In addition to its direct impact on diabetes-related research and manpower programs, the Administration's budget proposal is an ironic example of shortsighted policy, since the increasing economic burden of diabetes directly increases Federal expenditures for health care delivery programs.
- **National Diabetes Control Program—CDC:** The National Diabetes Control Program's budget of $6 million has not been increased for 3 years, despite inflation. Therefore, opportunities for continuing and extending the dramatic accomplishments summarized earlier and described in chapter 6 will not be exploited unless additional funds are provided. These advances are currently limited to demonstration projects within 20 states. The expansion of this effort within these states and an extension to additional regions of the country depend on additional resources.
- **Model Diabetes Care Program—IHS:** A unique initiative is under way within the Indian Health Service to develop diabetes control programs for a specific population with an unusually high prevalence of diabetes (see chapter 7). This very small program, with a current budget of $1.4 million, has gained the necessary experience to warrant a broader outreach of its activities within IHS. Health care expenditures for diabetes and its complications are rising rapidly within IHS, and additional resources are urgently needed to extend this preventive health care program.

RECOMMENDATIONS

The advances, needs, and opportunities summarized in this report justify a strengthened and expanded Federal diabetes program. The Board's budget recommendations (table 1) represent the minimum resources necessary to continue the program at the current level of effort and provide minimal additional support to essential priority activities.

Table 1

BUDGET RECOMMENDATIONS FOR DIABETES-RELATED PROGRAMS
(Amounts in Millions)

	FY 1984*	FY 1985
National Institutes of Health		
NIADDK	$ 93.2	$110.0
NHLBI	17.8	20.0
NEI	23.0	26.0
NICHD	9.4	11.0
NINCDS	7.3	8.5
NIAID	5.9	7.0
NIA	2.5	3.0
NIDR	2.3	2.5
NIGMS	1.0	1.1
NIEHS	.1	.2
DRR	17.8	20.7
Subtotal, NIH	$181.0	$210.0
Centers for Disease Control	6.0	9.0
Indian Health Service	1.4	1.9

* Estimated obligations.

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National Institutes of Health: *The Board recommends that Congress provide $210 million in fiscal year 1985 for diabetes and related research in the National Institutes of Health, including $110 million for diabetes activities in the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. The Board recommends a total budget of $550 million for all programs within NIADDK, including diabetes. This budget will restore full recommended support for noncompeting investigator-initiated research grants; permit funding of new research grants to the paylines and award rates realized during fiscal years 1977-80; and fully support diabetes centers, research manpower development programs, and other priority activities. The diabetes budgets recommended for other NIH Institutes (table 1) represent a comparable commitment to promising initiatives in their respective areas of responsibility.*

Centers for Disease Control: *The Board recommends that Congress provide $9 million in fiscal year 1985 to continue and expand the National Diabetes Control Program at the Centers for Disease Control. This amount includes funds to intensify efforts in the 20 current project states, to expand the program to five additional states, and to initiate high priority regional and national projects that will transfer program accomplishments to a wider area and population.*

Indian Health Service: *The Board recommends that Congress provide $1.9 million in fiscal year 1985 for the Indian Health Service to intensify efforts in the current five project sites, to expand to two additional sites, and to assist other service units that are ready to incorporate specific diabetes control approaches into existing health care programs.*

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2. DIABETES MELLITUS: AN OVERVIEW BASED ON RESEARCH AND CONTROL PROGRAMS

Our current understanding of diabetes mellitus, its etiology, clinical course, and complications, reflects significant advances both in research and in control programs. The exciting progress in research is the result of a large number of investigations in many diverse scientific disciplines. At the same time, well-planned diabetes education and control programs have begun to document reductions in hospitalizations and in some of the complications of the disease. As a consequence, the quality and duration of life of the diabetic patient has been improved in several areas. The savings in health care costs that could be achieved through full exploitation of these research and control advances easily exceed the Board's recommendations for Federal support of the entire national diabetes effort.

At the present time, 5 to 6 million Americans have diabetes mellitus, and an equal number may have the disease but have yet to be diagnosed. The annual economic burden of this disease, including the cost of medical care, time lost from work, and premature death, is $10 billion. It is impossible to estimate the cost of the emotional impact of the disease on the person with diabetes and on his or her family. The impressive progress that has been achieved through research and control programs provides greater opportunities than ever before to make significant advances in the control, cure, and prevention of diabetes and make reductions in the social and economic burden associated with the disease. The national program to combat diabetes is largely the responsibility of Federal agencies. It would be a catastrophe if this effort were not appropriately supported and expanded to realize its full potential of ultimately curing and preventing diabetes and its complications.

DIABETES MELLITUS: ETIOLOGY AND EPIDEMIOLOGY

Diabetes mellitus is a common, serious, and genetically predisposed familial disorder in which there are abnormalities in carbohydrate, protein, and fat metabolism. Although all diabetics have elevated blood glucose, diabetes is not a single disease. It comprises a variety of entities with different etiologies and clinical characteristics. The National Diabetes Data Group recently developed a classification and criteria for the diagnosis of diabetes that permits more meaningful comparison of data collected on all diabetic patients.

Two main types of diabetes occur in the American population. Type I, or insulin-dependent diabetes mellitus (IDDM), represents about 5 percent to 10 percent of the 5 to 6 million Americans with diabetes. This type usually develops in young individuals who have very little or no ability to secrete insulin and therefore must receive insulin treatment to maintain their health. However, the vast majority of diabetic Americans manifest Type II, or noninsulin-dependent diabetes (NIDDM). They usually develop the disease after the age of 40 and, although not totally deficient in insulin, are unable to secrete sufficient amounts to maintain normal carbohydrate metabolism. Insulin also is less effective in these patients.

Although diabetes is a familial disease with a strong genetic background, the genetic basis for the two types of diabetes is different. Extensive studies in identical twins with Type I diabetes indicate that factors other than genetics are important in this type of diabetes. In addition, epidemiologic studies both within the United States and elsewhere in the world have clearly indicated diversity in the incidence, clinical course, and characteristics of diabetes mellitus among different ethnic groups. For example, there is wide disparity in the prevalence of diabetes among different Scandinavian populations. Such studies indicate that unidentified environmental factors may play a significant role in the pathogenesis and course of diabetes. The elucidation of these factors provides important research opportunities for many national and international research and disease control organizations.

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Insulin-Dependent Diabetes Mellitus

Type I diabetes usually develops in individuals before the age of 30 but may occur at any age and is not associated with obesity. Although this type of diabetes is usually acute in overt onset, recent evidence suggests that antibodies to the insulin-producing cells (islet cells) may be present for a significant period of time prior to the development of symptoms of the disease. Such antibodies may participate in the destruction of the islet cells, leading to the complete absence of insulin production that characterizes patients with Type I diabetes. Research on the etiology of insulin-dependent diabetes mellitus has involved investigators in such diverse areas as genetics, immunology, virology, molecular biology, and epidemiology and has provided information that has broad applicability to diseases other than diabetes.

Type I diabetes may have a genetic component; more than 90 percent of diabetic patients have a specific pattern related to tissue transplantation antigens. The insulin-producing cells of these patients appear to be susceptible to inflammatory damage, leading to failure of insulin production. Such inflammation may result from attack by certain viruses, circulating antibodies against the islet cells, or other noxious insults from the environment. The identification of such factors provides an opportunity for designing approaches that could prevent the destruction of the islet cells. If specific viruses can be shown to be causative, a vaccine might be developed that would protect genetically susceptible individuals. Immunosuppressive therapy might prevent further destruction of islet cells in those individuals demonstrating islet cell antibodies prior to the clinical expression of the disease. This latter approach has been partially successful in an animal model of Type I diabetes.

Exciting progress is being made toward the transplantation of insulin-secreting tissue into patients with Type I diabetes. While rejection of the transplanted tissue continues to be the most serious problem, several experimental approaches have demonstrated that such tissue can be transplanted successfully across species barriers. Improved methodology is providing the larger numbers of islet cells from pancreas glands of larger animals and primates that will be necessary for islet transplantation in these species. An alternative to islet cell transplantation, segmental transplantation with vascularized graft, has been successfully accomplished in selected diabetic patients. The fundamental advances from this research have broad applicability to the transplantation of all tissues and are excellent examples of how diabetes-related research benefits many other areas.

Noninsulin-Dependent Diabetes

In contrast to patients with Type I diabetes, patients with Type II diabetes do not have complete absence of insulin production. They may have increased, normal, or decreased insulin secretion. Many etiologic factors are involved in Type II diabetes, which usually develops in later life. The genetic component of this type of diabetes is quite distinct from that observed in Type I diabetes.

Obesity plays a prominent role in patients with Type II diabetes. Insulin is less effective in these patients in facilitating glucose utilization in the three most important insulin-requiring tissues: muscle, fat, and liver. In addition to insulin resistance, patients with Type II diabetes also have a defect in insulin secretion in response to glucose. Since Type II patients are the vast majority of the diabetic population, and since obesity is a significant etiologic factor, current research emphasizes pathways of energy metabolism, appetite regulation, and the understanding and treatment of obesity. Improvement in glucose metabolism associated with weight control reflects both increased insulin secretion and more efficient action of insulin at the cellular level.

ROLE OF INSULIN AND OTHER HORMONES

It is obvious that abnormalities in both insulin secretion and insulin action are fundamental in patients with diabetes. The regulation of insulin secretion is complex, involving many factors such as energy utilization, interactions of other hormones, and a crucial role of calcium. Understanding this process may provide an explanation for and a therapeutic approach to the abnormality in insulin secretion in noninsulin-dependent diabetic patients. The gene controlling insulin synthesis has been identified and characterized. This information has led to the identification of several patients who have an abnormal insulin gene that results in synthesis of an abnormal insulin with altered biologic activity.

The initial action of insulin depends upon its association with specific molecules on the surface of the cell. These insulin receptors have been partially purified and characterized. Defects both at the level of the receptor and at subsequent steps in the cell are responsible for the insulin resistance seen in patients with different types of diabetes. Elucidation of the mechanism by which insulin acts could facilitate the synthesis of compounds for use in oral treatment.

Recently, the hormone that controls growth hormone secretion by the pituitary gland has been identified and synthesized. One of the most exciting and productive areas of research involves the

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demonstration of families of closely related proteins that are present in the brain, the gastrointestinal tract, and the pancreas and that play important roles in such diverse processes as appetite control, energy utilization, and hormone secretion. Glucagon and somatostatin are only two examples of the growing number of proteins known to play important roles in the regulation of carbohydrate metabolism.

The cloning of the human insulin gene and its insertion into bacteria now provides unlimited supplies of insulin with the same amino acid composition as human insulin. This remarkable achievement has been a model for the application of molecular biology to the treatment of human disease.

CHRONIC COMPLICATIONS OF DIABETES

The average life expectancy of the diabetic patient is significantly lower than that of a nondiabetic person due to the chronic complications of diabetes that affect the eyes, kidneys, and nerves and cause accelerated arteriosclerosis. These chronic complications are responsible for a major portion of the $10 billion economic impact of diabetes in this country. While significant research advances are being made concerning the etiology of these complications, their exact cause and relationship to control of blood glucose are unresolved. There is increasing impressive data from animal studies that indicate that some of these complications can be prevented, delayed, and even possibly reversed by meticulous control of blood glucose. The application of these exciting results to human diabetes is now in progress in several carefully designed, long-term clinical trials. The most comprehensive trial is the cooperative Diabetes Control and Complications Trial, initiated by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, involving over 250 patients with Type I diabetes. This study, currently in the feasibility phase, will examine the effects of meticulous blood glucose regulation on diabetic retinopathy and neuropathy and should also provide important data related to the other chronic complications of diabetes.

Consequences of metabolic abnormalities in diabetes may be important in the genesis of all the chronic complications. In the presence of hyperglycemia, glucose becomes attached to a variety of proteins and may alter or interfere with their function. The best example of this is the binding of glucose to one of the components of hemoglobin (hemoglobin A_{1c}). The measurement of this glycosylated hemoglobin provides an excellent indication of the degree of regulation of the blood glucose during the preceding several months. Other proteins that can be glycosylated similarly are found in the membranes of the kidney, eye lenses, and nerves. At present, the exact significance of such glycosylation in regard to function of these tissues is not clear but is under intensive investigation. In addition, hyperglycemia is associated with activation of a pathway of glucose metabolism (polyol pathway) that leads to intracellular changes that can interfere with the normal function of the cell. A variety of drugs that interfere with this pathway are being investigated intensively since they have shown a beneficial effect in preventing some of the chronic complications of diabetes, especially in the eyes and nerves, in experimental animals.

Etiology and Treatment of Diabetic Retinopathy

Diabetic retinopathy is a leading cause of new adult blindness in the United States, with 5,000 new cases occurring annually. More than 90 percent of Type I diabetic patients have some degree of retinopathy after 15 years of diabetes. This initial, mild stage does not significantly interfere with vision. However, after 20 years of diabetes, about 50 percent of these patients develop the more severe, proliferative stages that are associated with significant visual problems. While the risk of retinopathy is lower in patients with Type II diabetes, its development and progression may occur sooner. A recently completed clinical trial supported by the National Eye Institute (NEI) unequivocally established that laser photocoagulation decreases the risk of severe visual loss by 60 percent in diabetic patients with moderately severe proliferative retinopathy. Two ongoing NEI-sponsored trials are evaluating treatments at earlier (nonproliferative and mild proliferative) and later (severe proliferative) stages.

The initial abnormality of diabetic retinopathy occurs in the smallest blood vessels (capillaries), some of which become dilated and excessively leaky, while others become occluded. The fundamental cause of this vascular damage is unknown, but recent studies suggest that elevated glucose levels may damage vascular cells and impair regulation of blood flow. Sophisticated new techniques have been developed to study blood flow, and a clinical trial of an agent that may block the possible damaging effect of elevated glucose has been started. In addition, the impact of meticulous control of blood glucose on the development and progression of diabetic retinopathy is being assessed in the Diabetes Control and Complications Trial cited earlier.

Etiology and Treatment of Kidney Diseases

Patients with diabetic kidney disease now represent the single largest segment (about 25 percent)

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of patients entering end-stage renal disease programs. As a result of recent advances in both kidney dialysis and renal transplantation, diabetic patients are achieving survival rates in some centers that approach those of nondiabetic patients receiving similar treatment. Although the etiology of renal complications is poorly understood, studies in both animals and humans have demonstrated that some of the early changes in kidney function in diabetic patients can be reversed or prevented by stringent control of blood glucose. Hypertension and kidney infections also have an adverse effect on the progression of renal disease in the diabetic patient, emphasizing the importance and benefit of early detection and treatment of these conditions in delaying the progression of this complication.

Etiology and Treatment of Neurological Complications

Serious neurological complications involving both the sensory and motor functions of the peripheral and autonomic nervous system occur in up to 25 percent of all diabetic patients and are a significant cause of diabetic morbidity. Exciting and dramatic advances have been made recently that may explain the etiology of some neuropathy and its relationship to elevated blood glucose. Nerve tissue from diabetic subjects shows a significant decrease in myoinositol, a sugar-like component that is associated with impaired nerve conduction velocity. This decrease in myoinositol appears to result from elevated blood glucose, which interferes with the transport of myoinositol into the nerve. These findings support earlier observations that appropriate control of blood glucose improves nerve conduction velocity. Increased activity of the polyol pathway of glucose metabolism also appears to contribute to decreased myoinositol and nerve conduction velocity. Administration of a drug, sorbinil, which inhibits the polyol pathway of glucose metabolism, or use of large amounts of myoinositol has reversed both of these defects in experimental animals. Present drug treatments are usually unsatisfactory, and these exciting observations may provide the basis for successful treatment of diabetic neuropathy.

Etiology and Treatment of Arteriosclerotic Cardiovascular Disease

Patients with diabetes have an increased incidence and acceleration of arteriosclerosis that involve the large arteries to the brain, heart, and extremities. This condition is associated with increased incidence of strokes and heart attacks and need for amputations in persons with diabetes. Arteriosclerosis in diabetic patients is probably not different from that in people without diabetes, but occurs at an earlier age and progresses more rapidly. Although the exact cause of arteriosclerosis is obscure, many factors such as control of blood lipids and blood glucose appear to be important. The development of noninvasive techniques to assess the extent and progression of arteriosclerosis will permit an evaluation of the efficacy of current and future therapeutic approaches, including diet modification, drugs, and control of blood glucose.

Amputations are at least 15 times more common in people with diabetes because of the increased incidence of peripheral vascular disease and peripheral neuropathy. These conditions make the feet of the diabetic patient much more susceptible to trauma, infection, and gangrene and impede the healing of such lesions. In addition to an inadequate blood supply, the loss of sensation in the feet increases the potential for development of foot problems necessitating amputation. However, even in the absence of new treatment advances, amputations in diabetic patients have been significantly reduced following education and control programs that have systematically applied currently available information and treatment strategies. Even wider dissemination and implementation of appropriate foot care information to diabetic patients and their health care providers would further significantly decrease the incidence of such amputations.

ACUTE COMPLICATIONS OF DIABETES MELLITUS

While it is not established that the chronic complications of diabetes are a consequence of hyperglycemia, the acute complications of diabetic ketoacidosis and the problems of diabetes in pregnancy are clearly linked to insulin deficiency and hyperglycemia.

Diabetic Ketoacidosis

Patients with Type I diabetes are quite susceptible to development of diabetic ketoacidosis. This is frequently the initial event in the diagnosis of this type of diabetes. However, even after diagnosis and institution of therapy, many Type I diabetic patients have recurrent episodes of ketoacidosis precipitated by various stresses such as infections or emotional problems. While important advances have been made in the treatment of diabetic ketoacidosis, resulting in significant reductions in mortality and morbidity, these advances have not been widely implemented throughout the country. A diabetes control project under the auspices of the

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Centers for Disease Control demonstrated that patient education, early detection, and prompt and effective treatment significantly diminished serious diabetic ketoacidosis and reduced the number of associated hospitalizations. Obviously, the widespread dissemination of such programs would markedly reduce the frequency of diabetic ketoacidosis in both established and new diabetic patients.

Complications of Pregnancy Due to Diabetes

The importance and efficacy of insulin and the meticulous regulation of blood glucose have been exemplified best in the management of diabetes during pregnancy. The diabetic condition produces significant risks for both the mother and the fetus. A large number of pregnant women also develop a transient abnormality of carbohydrate metabolism (gestational diabetes), which disappears after pregnancy but is associated with a higher incidence of diabetes later in life. Each year, approximately 10,000 babies are born to diabetic women, and an additional 60,000 to 90,000 babies are born to women with gestational diabetes. These infants are more susceptible to spontaneous, unexplained intrauterine death, excessive size and weight, increased frequency of respiratory distress syndrome, neonatal hypoglycemia, and jaundice. The babies of women with previously existing diabetes have approximately a fourfold increase in congenital malformations.

Several large, carefully designed studies have unequivocally demonstrated that the meticulous control of blood glucose and intensive monitoring of the fetus during the second and third trimester of pregnancy reduced these complications, except congenital malformations, to levels approximating those in nondiabetic pregnancies. A preliminary study has provided evidence that institution of such meticulous diabetic control prior to and during the initial 12 weeks of pregnancy (when the organs are being formed) also can reduce the congenital malformation rate. The National Institute of Child Health and Human Development is currently conducting a large-scale cooperative clinical trial involving five university centers to provide definite information on this crucial issue.

Unfortunately, information about the effective management of the pregnant diabetic has not been widely disseminated and applied throughout the country, and the majority of pregnant women with diabetes are not benefiting from these treatment approaches. The application of known effective treatment methods could result in tremendous savings, since it costs $10,000 a week for intensive nursery care of infants and $1 million for the lifetime care of severely handicapped individuals. The lack of widespread implementation of these treatment strategies underscores the need for education programs for patients, physicians, and other health care providers.

IMPROVED TREATMENT MODALITIES FOR DIABETES

The exciting advances in basic and clinical research should eventually lead to improved approaches to the prevention and treatment of diabetes. In the meantime, however, several new developments, including those cited above, have already increased our ability to treat this disease. Widespread and effective application of these advances requires better and more comprehensive educational programs for both the diabetic patient and the health care provider. For this reason, the National Diabetes Advisory Board initiated the development of two important publications: *National Standards for Diabetes Patient Education Programs*; and *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners.* The latter publication provides guidelines for early detection and effective treatment of visual impairment, foot and kidney complications, acute hyperglycemia and ketoacidosis, and adverse outcomes in pregnancy due to diabetes.

In addition to the above advances in the prevention or clinical management of acute and long-term complications, the following treatment advances offer additional assistance to diabetic patients and their health care providers:

Self Blood Glucose Monitoring

Techniques now are available that permit patients with both types of diabetes to monitor their own blood glucose daily. These techniques permit patients to improve their control markedly by learning how the body responds to food, exercise, stress, and medication. For the first time, the person with diabetes can share with the physician accurate information on how the treatment plan is working. Patients become equal partners in decisions about treatment and learn to make appropriate adjustments on their own. Therapy can be truly individualized, and patients are motivated to improve their level of self-care by the immediate and ongoing feedback provided by self-monitoring of their own glucose levels.

Self blood glucose monitoring in Type I diabetes helps patients to avoid or correct the wide swings in blood glucose and the associated hazards of extreme hypoglycemia or diabetic ketoacidosis. The use of self blood glucose monitoring in Type II diabetes is particularly appropriate, since these pa-

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tients frequently do not have the usual symptoms of uncontrolled diabetes. Finally, self blood glucose monitoring is important for all diabetics because the renal threshold for glucose may have been compromised and hyperglycemia may be present even when urine tests are negative. Although self blood glucose monitoring is considerably more accurate and therefore more useful than urine testing, testing the urine for ketones is still important to prevent the development of diabetic ketoacidosis when blood glucose is consistently elevated.

While self blood glucose monitoring indicates the ambient blood glucose, determination of glycosylated hemoglobin (hemoglobin A_{1c}) provides the physician and the patient with an objective independent measure of the degree of blood glucose control during the preceding 80 to 100 days. This simple, inexpensive test provides an opportunity to correlate the degree of blood glucose control and the development and progression of diabetic complications.

Purified and Human Insulin

Recent technological advances have resulted in production of insulin that is more than 99 percent purified. Such preparations are much less antigenic and have significantly decreased the incidence of allergic reactions due to antibody formation. Loss of subcutaneous tissue at the site of insulin injection (lipoatrophy) has not been observed with purified insulin.

Probably the most dramatic application of basic research to diabetes has been the production of human insulin using recombinant DNA technology. This remarkable accomplishment has eliminated the dependence on animal pancreas glands and guaranteed an unlimited supply of insulin. Current research is examining newer insulin preparations whose activity will be coordinated with the changes in blood glucose.

Insulin Infusion Devices

In persons without diabetes, insulin is being constantly secreted at a basal rate with increased amounts at mealtimes. This physiologic system is not adequately reproduced by current methods of insulin administration, including multiple daily injections. Recently, the use of battery-operated insulin infusion devices has markedly improved blood glucose control in selected patients. These external pumps can be programmed to provide a constant basal rate of insulin with boluses at mealtime. The most recent pumps are small and light and have important features for safety and better control of blood glucose.

Significant progress has been made on insulin pumps that can be implanted under the skin and thus avoid the disadvantage of external devices. The initial implantable pumps could only provide a constant amount of insulin. More recently implanted pumps can also give boluses of insulin at mealtime using an external radio signal. The ideal implantable pump would consist of a glucose sensor that would constantly regulate the amount of insulin to be delivered depending on the level of blood glucose. Development of such a glucose sensor is the focus of current intensive research efforts.

Insulin infusion systems, whether external or implantable, may not be appropriate or necessary for all diabetic patients. Some patients have achieved a similar degree of blood glucose control utilizing multiple daily injections of insulin.

Transplantation of Islets

Neither multiple injections of insulin nor current insulin infusion devices provide optimal regulation of blood glucose. Transplantation of insulin-producing cells (islets of Langerhans) has the potential to restore carbohydrate metabolism to normal in patients with Type I diabetes. While this approach has been successful in animals, two problems have prevented its wide application to humans. The first problem is tissue rejection, and the second is the availability of sufficient amounts of insulin-producing tissue. Segmental pancreatic transplantation with a vascularized graft has successfully controlled blood glucose in selected diabetic patients. While this approach obviates the problem of sufficient islet cells, it is still susceptible to tissue rejection and the additional problem of damage from the pancreatic digestive enzymes.

The problem of tissue rejection is under very intensive investigation, and exciting progress has been made. Several different approaches have permitted successful transplantation of islet tissue across species in animals. These approaches have emanated from a much better understanding of immunologic processes in the body and are applicable to the broad field of organ transplantation. In addition, new and more potent immunosuppressive drugs are being developed that do not have the undesirable side effects of those currently available. Rapid advances also are being made in the technique of separating the insulin-producing cells so that sufficient amounts are obtained for transplantation. These new developments are now being applied to large animals and will probably be applied to humans in the not-too-distant future. Their successful outcome provides an opportunity to cure Type I diabetes and prevent its life-threatening chronic complications.

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Diet Therapy and Pharmaceutical Agents

Caloric restriction and weight loss are the optimal treatment for most patients with Type II diabetes who are overweight. Restoration of normal weight in such patients markedly improves their ability to metabolize carbohydrates both as a consequence of increased insulin secretion and of increased responsiveness to insulin. The composition of effective diets, the types of carbohydrate, and the optimal amount of fiber are being actively investigated.

Appropriate education programs and nutritional guidance are needed to assist obese Type II diabetic patients to attain their ideal body weight. A better understanding of the mechanisms of appetite control and energy expenditure, subjects of intensive research, will provide more effective therapeutic approaches to the very difficult problem of weight control. Not all patients with Type II diabetes, especially if they are thin, can obtain appropriate blood glucose control with diet therapy alone. Such patients may be treated satisfactorily with the oral hypoglycemic agents that acutely increase insulin secretion. In addition, these drugs may have other beneficial effects that improve carbohydrate utilization. Newer, more potent oral agents are being developed that may ameliorate the possible defects in insulin secretion and action that characterize Type II diabetes.

SUMMARY

Not since the discovery of insulin has the outlook for the person with diabetes been better. Biomedical research, both basic and clinical, is contributing significantly to our current understanding of the disease and the treatment advances that are now available. This knowledge must be widely disseminated and applied for the benefit of the entire diabetic population so that the economic and emotional burden of this disease can be markedly reduced and eventually eliminated. To this end, it is imperative that diabetes-related research and control programs be continued and expanded by both the Federal Government and other organizations.

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3. BIOMEDICAL RESEARCH

The ultimate goal of diabetes-related research is the prevention and cure of diabetes. As with many other serious diseases, however, the exact cause or causes of diabetes remain unknown. For this reason, diabetes research is proceeding simultaneously along two closely related pathways, each critically important to the health of our people. The objective of one pathway is to develop improved methods for treating diabetes and preventing or reducing the severity of its disabling complications. This approach provides immediately useful information of value to the millions of people already afflicted with diabetes and its complications. The second approach is to seek more basic and fundamental information concerning the etiologic and pathogenetic mechanisms of diabetes and its complications. Although this latter approach may not lead immediately to clinically applicable results, the information provides the foundation for the ultimate prevention or cure of the disease itself, as well as for more effective treatment of its complications.

Many advances have been made in each of these two major areas in recent years. To assess these developments and to identify directions for the future, the Board recently convened the Second National Diabetes Research Conference in Reston, Virginia. This conference, held in September 1983, was attended by approximately 160 leading scientists from across the country and overseas. Twelve workgroups were organized to focus on the major areas of diabetes-related research. In addition, plenary session speakers addressed recent developments in several fundamental research areas related to diabetes programs.

The findings and recommendations of these 12 workgroups were compiled and published earlier this year. The conference was an exciting commentary on the remarkable progress in both basic and clinical research. Significant advances have occurred in almost every area of investigation, ranging from a better understanding of the factors that underlie the etiology and progression of the disease and its complications to the development of improved methods for treatment that may prevent or reduce the severity of many of the complications of diabetes. Many of the conference findings and suggestions have been incorporated into this year's annual report.

We have clearly arrived at a crossroads in our effort to cure diabetes. Advances in service and technology have provided innumerable opportunities for future research advances and their application to all persons with diabetes. Unfortunately, these opportunities come at a time of continued and severe constriction in the research budgets of the Federal Government. For example, the percentage of approved investigator-initiated scientific research projects that can be funded by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases has declined sharply—from approximately 45 percent in recent years to approximately 33 percent in fiscal year 1984. This decline would have been even greater—to 27 percent—if the Institute had not administratively reduced previously awarded budgets for individual research grants and research centers. The Administration's proposed budget for FY 1985 would result in even further reductions. Similar constraints are impeding the activities of the other NIH Institutes responsible for diabetes-related research. These fiscal constraints obviously have a deleterious impact on the scope and effectiveness of the research that can be performed.

Each of the 12 workgroups at the Reston conference compiled a long list of unmet needs in their respective areas. These opportunities cannot be exploited within present resources. Considering the opportunities for significant future scientific advances in the treatment and, it is hoped, the prevention and cure of diabetes, it is clear that a greater investment in diabetes research is a sound and cost-effective initiative. The following summary of biomedical research accomplishments and future opportunities, therefore, represents both the optimism of the Board for the future and our increasing concern that these advances will not be extended because of unrealistic budgetary constraints placed upon the Federal agencies responsible for progress in the fight against diabetes.

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INSULIN-DEPENDENT DIABETES MELLITUS

Insulin-dependent diabetes mellitus occurs in individuals of all ages, but its peak incidence is in adolescence and youth. IDDM is associated with a marked loss of beta cells in the endocrine pancreas and a diminished ability to produce insulin.

IDDM shows consistent patterns of age-related onset, but the onset appears to vary with the seasons and between geographic areas. The disease develops primarily in individuals who have certain genes coding for transplantation antigens in the major histocompatibility complex present on the short arm of chromosome 6. Islet cell antibodies are present in the majority of insulin-dependent diabetic patients at the time of diagnosis, but the disease may have an asymptomatic phase of several years before symptoms and insulin dependence develops. The genetic and environmental factors that may control the pathological processes are not understood.

Accomplishments

- Studies continue to document remarkable variations in the incidence and prevalence of IDDM in children and adolescents in different parts of the world—for example, the incidence rate in Finland is more than 50 times greater than that in Japan.
- Although genetic factors may account for some of this geographic and cultural variability, environmental factors increasingly appear to be important in the etiology of IDDM.
- Epidemiological studies in the United States and Denmark suggest a decreased risk for the development of IDDM in children who were breast-fed as infants. These results, if confirmed, point toward possible early environmental factors that may protect against the development of IDDM.
- Geographic variation in clinical presentation has been observed. Diabetic ketoacidosis is frequently documented at initial diagnosis in North America and in northern Europe but is uncommon in southern Europe and Israel.
- Spontaneous partial clinical remission in the first several months after diagnosis is reported in approximately two-thirds of all patients and shows no significant geographic or racial variation.
- Research continues to provide new and exciting insights into the pathology of islet cell damage; the interface between genetic factors, autoimmunity, and noxious environmental agents such as viruses and pollutants; and the eventual expression of clinical diabetes.
- The HLA antigens DR3, DR4, or DR3/DR4 are present singularly or in combination in 90 percent of IDDM patients. Suggestive evidence points toward differing etiologies in the DR3 and DR4 associated diabetes.
- Molecular cloning techniques applied to the class II antigens indicate the probability of HLA subtypes, accounting for serological differences in HLA identical diabetic patients and healthy controls.
- HLA typing in healthy relatives of IDDM individuals has been shown to provide important predictive information of the risk of developing IDDM. The risk of developing the disease is 20 to 50 times greater among HLA identical siblings of IDDM patients compared to the general population.
- Several techniques for the detection of islet cell antibodies (ICA) have been devised, and all reveal that most newly diagnosed patients with IDDM have circulating ICA. However, there are some differences using these techniques, suggesting that the role of ICA in producing beta cell damage may vary in different patients.
- Two studies have found that the presence of ICA in the sera of healthy relatives of individuals with IDDM is an important predictor for the subsequent development of IDDM. These reports, as well as histological study of the pancreas in persons dying soon after the diagnosis of IDDM, point toward a prolonged asymptomatic phase of beta cell inflammation prior to the clinical expression of the disease.
- Preliminary studies have been performed using immunosuppression to prevent further beta cell inflammation in patients with recent onset of IDDM. A clinical trial utilizing cyclosporin A has been encouraging, suggesting that this therapy may produce an increased frequency of clinical remission.

Future Directions

Research efforts of the past few years have resulted in an exponential increase in our knowledge of the pathogenesis of IDDM. This growth pattern should continue to accelerate, if adequate support is provided. Since research into the etiology and pathogenesis of IDDM relates directly to the pre-

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vention of the disease, increased resources should be made available to expand efforts in this area.

- Further rigorous epidemiologic studies are needed to clarify the annual and geographic differences in incidence and the causes of these differences, which appear to be due to environmental factors rather than genetic variations.
- A continuing reassessment of the natural history of IDDM (i.e., its morbidity and mortality) is necessary in view of the rapidly changing methods of therapy.
- Techniques to probe the genetic basis of IDDM should be expanded to define better the molecular basis by correlating the serologic probes with gene sequences associated with IDDM and possibly even to unmask the precise gene defect itself, which appears to be related to gene products in the HLA-D region.
- Continued efforts should be made to define the precise role and relationship of viruses to IDDM in humans.
- Studies of autoimmune phenomena in strains of animals developing diabetes are needed to help in understanding the genetic basis for inheritance of disease susceptibility in humans and for guidance in approaches to intervening in the process leading to beta cell destruction.
- The detection of islet cell antibodies in assays, including immunohistocytochemistry on human pancreatic specimens with the use of living cells or fixed cells, requires standardization, exchange of control sera, defined precision, and increased reproducibility of assays. The results would permit a more rigorous assessment of the predictive value of a positive islet cell antibody test to the development of IDDM among otherwise healthy individuals. Studies of islet-cell-specific, cell-mediated immunity by modern techniques should be encouraged.
- Relevant antigens need to be isolated and characterized so they can be used in more specific and reproducible assays to detect and monitor beta cell destruction.
- Scientifically rigorous studies into the basic genetic and immunologic processes in autoimmune diseases should be expanded, encouraged, and enthusiastically supported in response to the major advances that have already been made, especially in animal models. Carefully and rigorously controlled studies are needed in humans to assess the role of the immune system in initiating the beta cell destruction leading to IDDM and the potential benefit and hazards of immunosuppressive therapy.

NONINSULIN-DEPENDENT DIABETES MELLITUS

The vast majority of Americans with diabetes manifest Type II, or noninsulin-dependent, diabetes mellitus. NIDDM is not a single disease but a heterogeneous group of disorders that are usually associated with decreased insulin responses to oral and intravenous glucose loads as well as a decrease in insulin's ability to stimulate glucose utilization. Although many patients with NIDDM are obese, the two conditions are not synonymous. Furthermore, it is apparent that environmental factors other than obesity can predispose the genetically susceptible individual to the development of NIDDM. However, the precise nature of the genetic-environmental interactions remains to be determined.

Accomplishments

- Evidence from identical twin studies has shown a powerful influence of heredity on the development of NIDDM.
- NIDDM is characterized by a decrease in insulin-stimulated glucose disposal. A variety of causes of this insulin resistance have been documented in patients, including decreases in the binding of insulin to its receptors, a reduction in the ability of insulin to stimulate glucose transport and glucose utilization by isolated adipocytes, and secretion of an abnormal insulin molecule.
- Techniques have been developed to quantify the degree of insulin resistance separately in the liver and peripheral tissues.
- Clinical research studies have shown that lowering blood glucose levels in patients with NIDDM can restore both insulin secretion and action toward normal.
- Evidence has been presented suggesting an association between an increased risk of developing NIDDM and changes in the flanking region of the insulin gene.
- Evidence that sulfonylurea compounds enhance insulin action at several steps suggests that the ability of these drugs to lower plasma glucose may not be totally due to their ability to stimulate insulin secretion.

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- It is known that significant differences in plasma glucose response can result from the consumption of equal amounts of different carbohydrate-rich foods. These findings have focused attention on the kind of carbohydrate to be included in diets for patients with NIDDM.
- It has been demonstrated that insulin-stimulated glucose disposal is enhanced in physically trained individuals.

Future Directions

Recent research has identified many important factors in the etiology and course of NIDDM. Since the vast majority of diabetes patients in this country have NIDDM, these promising leads must be pursued vigorously.

- An intensive search should be initiated for genetic and physiologic markers that may facilitate identifying the prediabetic state and determining the mode of inheritance of each form of NIDDM. These studies must be done in several different populations because of the likely genetic and environmental differences between these ethnic groups.
- Clarification of the genetic and physiologic significance of the restriction enzyme polymorphism in the flanking region of the insulin gene and a search for other such polymorphisms are needed.
- Further information is needed concerning the natural history and predictive value of impaired glucose tolerance (IGT). Efforts also should be made to determine whether progression from IGT to NIDDM can be prevented by weight control, drugs, dietary manipulations, or increases in physical activity or training.
- An increased understanding of insulin action at the cellular level is a prerequisite for defining the mechanism of insulin resistance in NIDDM. Such studies must be carried out in both animals and humans.
- Prospective studies, both in selected populations and in families, must be conducted in an effort to define the relationship between the defect in insulin secretion and action in the pathogenesis of NIDDM.
- There is a pressing need to develop more effective approaches to weight loss in obese patients who have NIDDM.
- Studies should be initiated in which *in vivo* insulin-stimulated glucose utilization is quantified in humans in conjunction with estimates of insulin action on its major target tissues—adipocyte, muscle, and liver. In this regard, methods are needed to study insulin action on muscle from humans.
- Better animal models for NIDDM and a means to make them available to investigators should be developed.
- Long-term studies of the effects of variations in the kind and amount of dietary carbohydrate and fiber on both lipid and carbohydrate metabolism must be performed.
- Since there is a close correlation between maximal aerobic capacity and the ability to dispose of dietary carbohydrate, attention should be given to improved physical training in NIDDM patients. Efforts must be aimed at determining if physical training can improve diabetic control.
- There is a need for further elucidation of the effect of sulfonylurea compounds at the cellular level, particularly on postbinding steps in insulin action.
- Attempts should be made to characterize people who do and do not respond to sulfonylureas, either acutely or after several months of therapy, to better understand the reasons for therapeutic failures. In addition, the potential synergistic effect of those compounds in combination with other possible hypoglycemic agents should be explored.
- Efforts must be directed to clarify the effects of intensive insulin therapy on subjects with NIDDM. Specifically: Which subjects should receive insulin therapy? Is weight gain inevitable and if weight is gained, does the change represent an increase in fat or lean body mass? What are the potential consequences, if any, of the prolonged hyperinsulinemia accompanying the intensive insulin therapy?

HORMONE BIOSYNTHESIS

Deficient production or secretion of insulin is a primary abnormality in IDDM and is also a factor in the etiology of NIDDM. The formation of insulin and the other pancreatic islet hormones, including glucagon, pancreatic polypeptide, and somatostatin, is a complex process requiring many steps before the final active hormones can be secreted. Recent research has revealed that the genes for these small peptide hormones encode larger precursor proteins, which are then cleaved to release the

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hormones as they are transferred to storage sites where they are readily available when secretory stimuli signal their discharge. Many transfer and processive steps are involved in generating not only the final hormone structure but also the appropriate messenger RNA molecules, which serve to convey the information stored in the gene to the protein-synthesizing systems of ribosomes. This information results in new concepts and techniques for better defining how disorders in the biosynthetic processes may be causally related to various forms of diabetes and provides the potential for unlimited supplies of insulin and other important biological products.

Accomplishments

- The complete structural analysis of the human insulin gene and its localization to a defined region on the short arm of human chromosome 11 have been defined.
- The structures of the genes for glucagon and somatostatin in humans and the complete structure of their precursor forms have been defined.
- A polymorphic region has been discovered in the DNA which is close to the insulin gene that may influence susceptibility to diabetes and may be a marker for IDDM or NIDDM.
- New forms of diabetes due to human insulin gene mutations have been discovered that result in the secretion of abnormal insulins with decreased biologic activity.
- Human and animal insulin genes have been transplanted and expressed in a variety of cultured noninsulin-producing cells.
- Certain DNA sequences near genes have been discovered that may enhance (or inhibit) their transcription under certain conditions. The possible role of these sequences in regulating insulin gene expression is being explored.
- New insights have been gained into molecular processes that allow secretory products to be formed.
- Further progress has been achieved in identifying and characterizing the processing enzymes for the conversion of precursor forms such as proinsulin and proglucagon into active products.
- Biosynthetic human insulin has been introduced into diabetes therapy—the first important medical product of genetic engineering to reach widespread clinical application. Production of human proinsulin also has been achieved in bacterial host cells.
- Evidence has been found for the production of other potentially bioactive peptides, in addition to pancreatic polypeptide, somatostatin, and glucagon from their respective cells of origin in the pancreatic islets.
- The genes for preprorelaxin (an insulin-related peptide hormone from the corpus luteum of the ovary) and the IGF (the insulin-like growth factor) have been isolated by recombinant DNA techniques.

Future Directions

The extraordinary progress in understanding gene structure and function offers exciting opportunities to make fundamental advances in many areas related to the etiology, prevention, and treatment of diabetes.

- Insulin gene mutations and polymorphisms should be studied in greater detail to define more precisely their role or roles in the pathogenesis of diabetes mellitus and to gain a better understanding of structure-activity relationships within the insulin molecule and its precursors.
- Systems should be explored for controlled expression of insulin genes in cells suitable for transplantation into patients.
- Improved understanding is needed of the role of glucose and other regulators of insulin gene transcription and preproinsulin mRNA translation in beta cells, including the potential regulatory roles of both DNA and mRNA modifications in these processes, especially as they relate to insulin secretion in NIDDM.
- More information is needed on many important aspects of hormone biosynthesis and secretion, such as secretory peptide segregation, intracellular transport, sorting from proteins destined for other roles, and enzymatic conversion to hormonal products, as well as the identification of new defects in these processes.
- Functional and structural relationships among the bioactive peptides of the pancreas, gastrointestinal tract, and nervous system continue to emphasize the broad role of peptide hormones that are important to diabetes. Further investigations of these potentially important effectors (and on their respective genes) should be encouraged.
- Improved methods should be developed for the biotechnological production of important proteins and peptide hormones related to

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diabetes research—for example, human growth hormone, insulin-like factors, and islet cell trophic factors. Of particular interest are potential hosts other than *Escherichia coli*, including yeast, other strains of bacteria, or plant cells.

INSULIN SECRETION

The mechanism by which beta cells store and secrete insulin is central to all types of diabetes. In IDDM, a better understanding of beta cell membranes, organelles, and metabolic components may lead to methods designed to minimize the sensitivity of beta cells to viral or chemical attack. In all forms of diabetes, nutrition, stress, other hormones and neurohormones, and brain peptides act on insulin secretion from the beta cell and influence the intensity of the disease. Many of the current efforts to understand the etiology and to improve the treatment of diabetes, including transplantation, insulin delivery pumps, and new oral agents, arise from studies of islet cell physiology.

Accomplishments

- New evidence shows that compartmentalization regulates insulin secretion. Thus, intercommunication of islet cells shields certain cells from the secretions of neighboring cells, and newly synthesized insulin can be released preferentially over older storage forms, a process regulated by fuel substrates.
- Electrophysiological studies indicate that electrical and ionic events are integral to the secretion event. New research methods are providing highly sensitive approaches for analyzing the cascade of events between the signals initiated by a secretagogue and insulin release.
- Various general cellular mechanisms have been implicated in the insulin-release mechanisms: the phosphate potential, redox potential, islet pH, cyclic AMP, and various ion channels and pumps that handle calcium, potassium, sodium, magnesium, and zinc.
- The hormone secretory activities of the various types of islet cells are modulated by a diverse group of protein hormones (particularly from the gastrointestinal tract and the brain) and neurotransmitters via the autonomic nervous system. The abnormal somatostatin, glucagon, and pancreatic polypeptide responses in diabetes often can be normalized by intensive insulin treatment.
- Insulin secretory responses are modulated by a diverse group of substances that include fuels (glucose and amino acids), other hormones, and pharmacologic agents. These responses may be mediated by alterations in receptors for these substances on the islet cell surface membrane, their intracellular metabolism, or activation of various intracellular enzymes.
- Though rare, several cases of genetic beta cell defects resulting in the secretion of an abnormal insulin or the inability to convert proinsulin to insulin because of abnormal amino substitutions have been reported.
- Use of insulin clearance rates together with the measurement of C-peptide levels in blood are permitting better use of blood insulin levels to evaluate beta cell secretion.
- Control of hyperglycemia by diet, sulfonylurea, and exogenous insulin therapy has been shown to improve the impaired beta cell function in many patients with NIDDM. Thus, the reduction of "glucose toxicity" may have extended beneficial effects in these patients.
- Rich sources of beta cells are becoming available for experimental study. These sources include several new beta cell tumor lines with varying sensitivity to glucose and disbursed beta cell preparations from normal islets.
- Improved cell fractionation techniques afford the opportunity to examine the various organelles in the beta cell, including granule membranes, mitochondria, and microsomes, in an attempt to determine the function of these subcellular constituents in hormone secretion.

Future Directions

If the pathogenesis of the various forms of diabetes is to be understood and more rational therapeutic approaches discovered, more knowledge of the biochemistry, physiology, pathology and regulation of insulin storage and secretion is necessary.

- The precise mechanism by which metabolic fuels, other hormones, neural influences, and pharmacologic agents such as the sulfonylureas control insulin secretion and the secretions of the other islet cell types needs to be elucidated. Research should include the identification and characterization of their receptors, their intracellular metabolism, and changes in enzymes, cofactors, and phosphorylated proteins.

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- Monoclonal antibodies against islet membrane proteins are needed to understand membrane-protein relationships that regulate the secretory processes.
- The nature of islet cell anatomy, including vasculature, polarity, heterogeneity, nerve communication, gap junctions, and other systems of islet cell-cell communication, should be further elucidated.
- The integrated role of intracellular organelles (microtubules, microfilaments, granule membranes, etc.) on the compartmental storage and secretion of insulin should be defined. Microtechniques in single cells also should be developed for such studies.
- Continued development is needed of well-characterized, reproducible beta cell tumor preparations of isolated and purified islet cells with secretagogue sensitivities similar to normal cells.
- Well-characterized, reproducible animal models are needed to demonstrate modified insulin secretion.

HORMONE ACTION

The control of blood glucose and the balance among many metabolic pathways are precisely coordinated by a variety of hormonal systems. The major hormone that regulates glucose is insulin. The deficiency of insulin effect in the diabetic patient has a profound impact not only on blood glucose but also on all the tissues of the body. The effects on the tissues may play a major role in the long-term complications of diabetes.

In the diabetic state, changes occur in the levels in many other hormones, including the peptide hormones (glucagon, growth hormones, and somatomedins), steroid hormones (cortisol, estrogen, and progesterone), thyroid hormones, and catecholamines. Many of these are viewed as anti-insulin hormones since they antagonize insulin action. The control of blood glucose throughout the day represents a delicate balance between insulin and the "counter-regulatory" hormones. The study of hormone action, therefore, includes investigative activities in many areas of biomedical research.

Accomplishments

- Using sophisticated biochemical, biophysical, and morphologic techniques, researchers have made substantial progress in elucidating the structure and function of several hormone receptors, including the insulin receptor.
- Progress has been made in elucidating the early events in hormonal signaling of cells and in studying the effects of hormones on cell membranes, cellular enzymes, and events in the cell nucleus.
- The insulin receptor and the beta-adrenergic receptor for catecholamines have been purified to homogeneity, and their structures have been described. The insulin receptor consists of two subunits, one that binds insulin and the other that transmits an intracellular signal via protein phosphorylation. The beta-adrenergic receptor is a single protein that is capable of interacting directly with membrane components.
- Researchers have further characterized the chemistry and effects of possible "mediator" substances involved in insulin action.
- Both insulin and alpha-adrenergic catecholamines have important effects on calcium flux into cells that may link their action to a number of calcium-sensitive enzymes and to turnover of phospholipids.
- Diabetes in animals is associated with a decrease in the number of glucose transporters in some insulin-sensitive cells and a decrease in insulin's ability to stimulate translocation to the cell membrane.
- An important new regulator of intracellular metabolism has been indentified. This regulator, fructose 2,6-bisphosphate, appears to play a key role in the action of several hormones on intracellular lipid and glucose metabolism.
- The direct effects of insulin have been demonstrated on nuclear function and control of gene expression using the new techniques provided by molecular biologic research.
- Studies of hormone action in tissues involved in diabetic complications, particularly the vascular endothelium, have revealed the presence of hormone receptors and hormone effect.
- Alterations in the levels of certain insulin-like growth factors have been found in diabetic patients, and some of these have been shown to improve with diabetic control.
- Additional components of the adenylate cyclase system and their role in the hormonal regulation of cellular cyclic AMP concentrations have been elucidated.

Future Directions

Studies have yielded important information about several key aspects of hormone-induced cellular

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signaling mechanisms. New technologies will allow the effective pursuit of state-of-the-art questions related to cellular events at the levels of surface membranes, intracellular domains, and nuclear compartments. The stage of scientific pursuit in this field is fertile and engaging.

- The finding that the insulin receptor is an insulin-activated enzyme provides a possible mechanism of insulin action. Further studies of this process and of the putative mediators could lead to a true understanding of the mechanism of insulin action.
- The characterization of possible abnormalities in insulin receptor transduction in diabetes should provide a potential site for pharmacologic attack on diabetes and related disorders.
- An increased understanding of the chemistry of the insulin receptor and mediators should allow molecular genetic probes of these substances and their synthesis by recombinant DNA technology.
- Isolating glucose transporters and understanding their regulation are of utmost importance in diabetes and could lead to possible pharmacologic manipulation of this process.
- Insulin action is modulated by other hormones and neurotransmitters, which also have the cell membrane as their initial site of action. Further studies of these membrane-associated processes may help explain the interaction of the hormones that control glucose homeostasis.
- The precise relationship between phospholipid turnover, calcium flux, and hormone signaling can be studied with new focus.
- The application of contemporary techniques of molecular biology to the mechanism of action of peptide hormones has lagged behind that of steroid hormones. It is now clear that these hormones, including insulin, exert effects in the regulation of a specific gene, representing an area with tremendous potential for further knowledge.

INSULIN-DELIVERY SYSTEMS

At the present time, there is no known cure for diabetes. Its treatment consists of attempts to maintain blood glucose levels as near normal as possible without incurring unnecessary risks of hypoglycemia. This goal is seldom attained among most Type I, or insulin-dependent, patients and may result in the occurrence of serious acute, intermediate, and long-term complications. It is currently assumed that the desired degree of control of carbohydrate metabolism will simultaneously restore normal usage of fat and protein, which in turn will result in the elimination of all associated complications.

The recent development of highly purified insulins, including human insulin, has provided a very sophisticated form of medication that continues to be delivered by relatively primitive techniques. The identification of normal patterns of insulin secretion by the pancreas has stimulated efforts to supply or "pump" insulin into the body in a physiologic manner. These efforts coincide with the increasing number of patients now seeking improved methods to obtain better metabolic control.

Accomplishments

- Extensive efforts over the past decade using both "open" and "closed" loop insulin delivery systems have demonstrated the feasibility of such devices. Efforts in this area are continuing, and significant progress is being made on several fronts. A wide selection of external insulin infusion pumps is available.
- Over 100 insulin delivery pumps have been implanted in humans in carefully controlled investigational settings. Both Type I and Type II diabetics have received these implants, with the longest functioning for 3 years. (Preliminary evidence on the prevention of kidney deterioration in experimental animals treated with implanted pumps is encouraging.)
- For those who are unwilling to use a pump or to take more than two injections a day, a new pocket microprocessor device has been developed that calculates insulin dosage on a twice daily basis.
- New alternate modes of insulin delivery are being suggested, such as administering insulin via a nasal spray.

Future Directions

- Evidence from studies in humans and animals indicates that normalization of blood glucose will prevent or ameliorate some of the complications of diabetes. The effective transfer of this knowledge to the diabetic patient by trained professionals should greatly enhance the benefits attainable from the recent progress in biomedical research.
- Further basic and applied research is needed to develop new insulin preparations suitable for use in external and implantable insulin delivery devices.

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- Basic and clinical research is required to further clarify the effect of multiphasic and oscillatory insulin secretion on the short- and long-term advantages and disadvantages of subcutaneous, intravenous, peritoneal, and other routes of insulin delivery.
- Implantable insulin infusion systems should be developed and tested further while new design configurations, catheters, and safety features are evaluated. The development of glucose sensors, both external and implantable, should be a long-range goal.
- Further research is needed to determine and compare the relative risks of conventional forms of insulin delivery with the risks of intensive or investigative approaches to insulin delivery.
- Standardized methods of assessing diabetic complications must be developed. A surveillance mechanism and an established international registry for patients started on implanted insulin delivery devices must be strengthened.
- Expansion is needed of the clinical, technological, educational, and computer-assisted facilities required for quality health care delivery specific to insulin delivery systems.

TRANSPLANTATION

Injection of insulin through conventional methods or via infusion devices does not necessarily provide optimal regulation of blood glucose. Pancreatic transplantation to maintain insulin secretion holds the promise of providing the diabetic patient with optimal metabolic regulation through physiologic control mechanisms. Remarkable advances on multiple fronts have brought islet transplantation to the threshold of application to human diabetes. These advances will have a broad applicability to tissue transplantation in general.

Accomplishments

- Passenger leukocytes within islet grafts have been identified as being, at least in part, responsible for the initiation of rejection of islet transplants in small and large animals.
- Five methods have been developed for the destruction or alteration of passenger leukocytes in islet grafts that prevent rejection without the use of immunosuppressive drugs in the recipients.
- Two methods have been developed for the production of a tolerant status in recipient animals, permitting successful transplantation of untreated islets. The tolerant status was induced by small transfusions of donor blood into the recipients prior to transplanting the islets. The donor blood had been treated to remove or alter specific types of passenger leukocytes.
- Continuous-flow electrophoresis is a new apparatus that shows promise for separating and purifying adult and fetal islet cells.
- The optimum site for transplantation of islets in humans is one that is safe, easily accessible, and from which insulin is released from the islet grafts into the liver. The omentum in the abdomen fulfills these criteria and has been used successfully for islet implantation in animals.
- Studies in animals have shown that islet transplants will prevent, reverse, or arrest the early complications of diabetes involving the eyes, kidneys, and autonomic nervous system.
- In selected Type I diabetic patients receiving immunosuppression, transplantation of a segment of the pancreas with vascular attachment has successfully restored normal glucose metabolism. However, delayed graft failure after several months remains a major problem.

Future Directions

Recent advances in research clearly indicate that human islet transplantation is on the horizon. However, the results of segmental pancreatic transplantation in identical twins have raised potential new problems. Since the donor and the recipient were identical twins, immunosuppressive therapy was not necessary to prevent classical tissue rejection. The initial excellent control of the blood sugar was not maintained, and biopsy of the pancreas demonstrated infiltration and destruction of the beta cells over a 6-month period. These results indicate a highly specific cytotoxic lymphocyte "memory," persisting for at least 15 years in some diabetic patients, which may adversely affect the outcome of transplantation, whether it involves isolated islets or segmental pancreas. Additional basic and applied research now is needed to assure that biomedical advances are applied to human islet transplantation in a safe, reliable, and reproducible manner; that the transition to humans is accomplished as rapidly as possible; that the ultimate goal is attained of determining whether human islet transplantation will prevent or arrest diabetic complications; that the immunobiology of preventing rejection is under-

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stood more fully and applied to other tissue and organs; that human pancreas glands are made available for islet isolation; and that the methods and technology of human islet isolation are developed further for large-scale clinical islet transplantation.

THE COMPLICATIONS OF DIABETES

The complications of diabetes remain the major cause of morbidity and mortality among people who have the disease. Most of these complications, especially the alterations in peripheral nerves and the maternal and fetal complications of diabetic pregnancies, appear to be related to the effects of the derangement of metabolism on tissue growth. This situation may reflect increased glucose levels, decreased insulin action, or other biochemical abnormalities, including malfunctioning enzymes or intracellular environment. The vascular abnormalities encompass microangiopathy and macroangiopathy. Microangiopathy, or the degenerative changes of small blood vessels, underlies diabetic retinopathy and kidney disease. Macroangiopathy affects the large arteries and can result in myocardial infarctions, cerebrovascular disorders, and peripheral vascular disease. Research into the causes of these complications, as well as their treatment, prevention, and cure, is a fundamental part of the overall effort to combat diabetes.

KIDNEY COMPLICATIONS

Uremia, the result of progressive diabetic nephropathy, is the dominant clinical complication of long-term Type I diabetes. Renal failure caused by diabetes is the most prevalent diagnosis in adults who begin maintenance hemodialysis or who undergo renal transplantation. At least 25 percent of new dialysis patients are diabetic. As older patients are accepted into end-stage renal disease treatment programs, the number of Type II diabetics will definitely rise, increasing even further the proportion of dialysis patients whose primary disease is diabetes. Renal disease in these latter patients has received only rudimentary study. The cost of care for the uremic diabetic patient will approach $2 billion a year by the end of this decade. The proportion of this figure currently available for research to prevent kidney complications of diabetes is excessively small.

Accomplishments

- Dialysis teams in a few centers have increased the 4-year survival rate in diabetic patients from 40 percent to 70 percent. Some transplant teams have demonstrated that the 2-year patient and graft survival for diabetic and nondiabetic patients need not be different and that long-term, high-quality existence following successful transplantation is possible in the majority of patients.
- Preliminary studies in diabetic humans indicate that some of the very early kidney changes can be reversed with rigorous control of blood glucose and can be delayed with treatment of hypertension. However, the effectiveness of these treatment regimens declines rapidly with each successive stage in the course of diabetic glomerulopathy.
- Studies have demonstrated that islet cell transplantation and normalization of metabolism can reverse or prevent some kidney changes in diabetic animals.
- A better understanding has been achieved of the alterations in renal physiology that result from hyperglycemia, particularly changes in renal blood flow and capillary permeability, which may contribute to the development of kidney failure.
- The natural history of diabetic nephropathy in humans is better understood and may be described as follows: Urinary albumin excretion rates above 50 mg per 24 hours predict with a high degree of accuracy the ultimate development of overt clinical diabetic nephropathy, and expansion of the glomerular mesangium is the major structural lesion related to the development of overt diabetic nephropathy.
- Guidelines for the detection and clinical management of diabetic nephropathy have been included in *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners.* The emphasis of these guidelines is on the early application of currently available preventive measures or treatments.

Future Directions

- Present studies on the relationship between metabolic control of diabetes and nephropathy must be extended.
- The dramatic improvements in diabetic patients who undergo dialysis or transplantation remain limited to a few centers; other centers continue to report less optimistic results or exclude uremic diabetic patients from treatment. Greater effort is required to transfer information about effective treatment to more health professionals and patients.

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- Coincident multisystem disease complicates treatment protocols for the uremic diabetic patient. Especially troublesome are eye, gastrointestinal, cerebrovascular, and peripheral vascular diseases. Rehabilitation programs employing dialysis or kidney transplantation require better coordination between diabetologists, nephrologists, transplant surgeons, ophthalmologists, dialysis and transplant nursing and technical personnel, dietitians, and social workers.
- Further tests must be designed to unmask early glomerular injury so the treatment of hyperglycemia and hypertension can be instituted at an optimum time.
- The role of vasoregulation and glomerular capillary wall function should be intensively investigated using modern techniques and suitable experimental models. By defining precisely altered vasoregulatory and glomerular capillary wall function in the diabetic patient, alternate therapeutic avenues may be opened.
- Studies are needed of the regulation of synthesis and degradation of glomerular matrix components, including collagen-like moieties, fibronectin, and proteoglycans in whole glomeruli and isolated subpopulations of glomerular cells.

EYE COMPLICATIONS

In spite of important recent advances in the treatment of diabetic retinopathy, diabetes remains one of the leading causes of visual loss in the United States. Blindness is 25 times more common in individuals with Type I diabetes and 2 to 3 times more common in patients with Type II diabetes than in the age-matched nondiabetic population. Progress is continuing in this critically important field, both in research and in clinical treatment.

Accomplishments

- Long-term followup has confirmed earlier reports that photocoagulation can reduce the risk of blindness from moderately severe proliferative diabetic retinopathy by 60 percent. Clinical guidelines on this subject are included in *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners*, published by the Board. A trial of photocoagulation and of aspirin in earlier stages of retinopathy is under way.
- A clinical trial of the vitrectomy operation in the very severe stage of proliferative retinopathy is nearing completion. This study will determine the optimal timing for surgical removal of the extensive newly formed blood vessels and scar tissue in an attempt to reduce the risk of blindness from subsequent retinal detachment and vitreous hemorrhage.
- Epidemiologic studies have documented associations between the severity of retinopathy and age at diagnosis, sex, glycosylated hemoglobin, blood pressure level, and presence of nephropathy.
- Increasing evidence suggests that a fundamental factor in the pathogenesis of diabetic retinopathy may be an adverse effect of hyperglycemia on retinal vascular autoregulation. Retinal vascular reactivity has been shown to be impaired prior to visible retinopathy in experimental diabetes and in induced hyperglycemia in normal animals.
- An important new animal model of retinopathy that is seemingly identical to that of diabetes has recently been developed in nondiabetic dogs fed a diet rich in galactose. The animals had elevated glycosylated hemoglobin levels but had normal levels of blood glucose, insulin, free fatty acids, and cholesterol. These results suggest that the elevation of blood sugar (either glucose or other hexoses) may be an important determinant of retinopathy.
- The enzyme aldose reductase has been found in the intramural pericytes of retinal capillaries. The thickening of capillary basement membrane both in diabetic and galactosemic rats is inhibited by aldose reductase inhibitors. These and the above findings in dogs suggest that the alternative metabolic pathway for glucose, known as the polyol pathway, may be an important mechanism underlying diabetic retinopathy. The possibility of blocking this mechanism pharmacologically, and thus preventing or slowing the development of retinopathy, is being investigated in a large-scale clinical trial.
- Recently developed methods for noninvasive measurement of retinal blood flow provide new opportunities for investigating this important characteristic of the retinal circulation.
- Progress continues in understanding the process of intraocular neovascularization, with identification of a retina-derived angiogenic substance and demonstration of inhibitory activity in extracts of vitreous and cartilage.

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Future Directions

Although important progress has been made in developing and validating treatment for diabetic retinopathy, current treatments do not help all patients nor do they address the apparently fundamental problem underlying proliferative retinopathy — the closure of normal retinal vessels. Progress in biochemical, physiological, and cellular studies has been delayed by the paucity of animal models and by the long-term nature and great cost of investigations using them. Greater investment in basic research is needed if treatment for diabetic retinopathy is to go beyond its current empirical stage and become more uniformly successful.

- Research on the pathogenesis of diabetic retinopathy using animal models should be expanded and given special emphasis, particularly:

  — detailed characterization of the defects in blood-ocular barriers reported in diabetic individuals and experimental animals;

  — studies to delineate the role of the polyol pathway and glycosylated proteins in diabetic retinopathy;

  — biochemical studies of retinal capillary cells (in freshly isolated vessels and in tissue culture) to determine factors controlling their metabolism, proliferation, differentiation, senescence, and death; and

  — studies of the cellular and biochemical events involved in the development and evolution of intraocular neovascularization, "fibrous" proliferation, and traction retinal detachment, including the development of animal models.

- Strong support should continue for randomized clinical trials of treatments that may prevent or slow the development of diabetic retinopathy, as well as those which aim to prevent or reduce visual loss in patients with more advanced retinopathy.

- Clinical studies using newer noninvasive techniques to measure retinal and choroidal blood flow at rest and in response to stress, as well as vascular permeability, should be applied to groups of diabetic patients carefully chosen on the basis of the type and duration of diabetes and the stage of retinopathy, using standard epidemiologic techniques. Psychophysical and electrophysiological tests should also be applied to study the effects of metabolic and vascular abnormalities and to evaluate the effects of treatment on visual functions.

- Epidemiologic investigations including prospective studies, case-control studies, and population-based surveys should be given high priority to identify risk factors for the development of ocular complications of diabetes, to provide insight into their pathogenesis, and to define more clearly the public health problem posed by diabetic eye disease.

- The development of improved instrumentation and techniques to assist visually handicapped people in using their remaining vision should be encouraged.

CARDIOVASCULAR COMPLICATIONS

Atherosclerosis continues to be a major complication of diabetes. The diabetic condition doubles the risk of death from atherosclerosis and quadruples the risk for peripheral arterial disease. It is not yet clear whether diabetes is associated with a unique atherogenic factor or merely aggravates other atherogenic factors. Thus far, no single cause for the accelerated atherosclerosis in diabetic patients has been identified. Hence, a review of this field must consider not only diabetes itself, but also atherogenesis in general. In this context, the following major areas of progress have occurred:

Accomplishments

- It is apparent that the lipoprotein classes are more heterogeneous than previously thought, and new subclasses have been identified that may play a crucial role in the genesis of atherosclerosis.

- Evidence from a large-scale prospective study has indicated that reduction of serum cholesterol levels can reduce the incidence of coronary artery disease.

- Specific cell-surface receptors have been identified that recognize apoproteins present on various circulating lipoproteins, and researchers have established that this interaction is important in determining the metabolic fate of these particles.

- Several modifications of apolipoprotein composition, either *in vivo* or *in vitro*, have been shown to change the manner in which lipoproteins are bound and degraded by cell-surface receptors of various cell types. In some instances these modifications have led to the accumulation of intracellular lipid and the development of foam cells similar to those present in a developing atherosclerotic plaque.

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- A marked decrease in the rate of cholesterol efflux occurs when fibroblasts are cultured in the plasma of patients with NIDDM (compared with nondiabetic people), and this situation is associated with an increase in plasma apo-E concentration. Both the decreased cholesterol outflow from cultured cells and the elevated apo-E concentrations were rapidly reversed when NIDDM was well controlled with exogenous insulin.
- Several studies have suggested that hyperinsulinemia may be important in atherogenesis. These findings may influence some approaches to aggressive insulin therapy in NIDDM.
- The role of hyperglycemia itself as a risk factor for atherogenesis remains unclear. However, there is evidence suggesting that the outcome of vascular occlusion, particularly of strokes, may be worse if hyperglycemia exists.
- It has become increasingly possible to evaluate macrovascular disease by noninvasive methods. These methods have included Doppler velocimetry of the peripheral arteries, ultrasonic Duplex scanning of the carotid arteries, and radionuclide angiography. These techniques not only permit easier diagnosis but also provide data for broader ranging and more accurate epidemiologic studies.
- The role of platelets and of eicosapentanoids in atherogenesis is increasingly recognized, although the effects of diabetes on them is less clear.
- Techniques have been developed to measure the mechanical stresses produced by blood flow on vessel walls.
- The increased incidence of peripheral vascular disease associated with diabetes makes the feet of diabetic patients much more susceptible to infection and gangrene leading to amputation. Guidelines for the prevention, detection, and clinical management of this condition are included in *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners*, published by the Board.

Future Directions

New research methods and the increased knowledge base in the biomedical field will permit a more penetrating exploration of the processes leading to atherosclerosis in general. It will now be possible to test how diabetes affects atherogenesis. Through the combined use of epidemiologic methods and pathophysiologic approaches, it will be possible to generate and test hypotheses that may explain the accelerated atherosclerosis in diabetic patients.

- A better definition of functionally distinct lipoproteins is necessary to study their epidemiologic and pathophysiologic links to diabetes and to atherosclerosis.
- New epidemiologic trials such as the Diabetes Control and Complications Trial should be initiated to explore the effects of controlling hyperglycemia, hyperlipidemia, and hyperinsulinemia on macrovascular disease in diabetes.
- New noninvasive vascular assessment methods should be used to provide a more precise definition of the presence and extent of human macrovascular disease. For example, such techniques will permit a more precise definition of the effects of diabetic control on the progress of macrovascular disease.
- The interactions of platelets with the vessel wall and the effects of diabetes on these processes should be explored.
- More data are needed on the effects of diabetes on eicosapentanoids and on the ability of agents such as aspirin to block their atherogenic effects.
- The effects of diabetes on the mechanical stresses on the artery wall should be assessed.
- A better understanding is needed of the effects of insulin and glucose on vascular metabolism.

NEUROLOGICAL COMPLICATIONS

Disabling neurological complications are present in approximately 25 percent of the diabetic population in the United States. These complications involve both the sensory and motor functions of the peripheral nervous system as well as the autonomic nervous system, which controls the function of many internal organs. Diabetes also can affect the central nervous system because the accelerated atherosclerosis associated with the disease predisposes patients to stroke.

Exciting and dramatic advances have been made recently that may help to explain the etiology of some neurological complications of diabetes and their relationship to elevated blood glucose. These advances could provide the basis for better treatment regimens in the future.

Accomplishments

- Hyperglycemia is associated with three discrete metabolic abnormalities in peripheral

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nerves: decreased myoinositol content, increased polyol (sorbitol) pathway activity, and increased nonenzymatic protein glycosylation. The significance of these biochemical defects has been explored in diabetic animal models. Studies with these animal models suggest that alterations in myoinositol and polyol metabolism may provide a biochemical link between the diabetic state and nerve dysfunction. These findings link the two most commonly cited biochemical hypotheses for diabetic neuropathy to defects in nerve function and perhaps structure, thereby providing a cohesive pathogenetic scheme for diabetic neuropathy.

- Major abnormalities of axonal transport have been discovered in experimental diabetic neuropathy. At the same time, there have been important advances in understanding the mechanism of transport and in developing new technology for studying transport in normal and diseased nerves.
- Patients with IDDM frequently have deficient glucagon and epinephrine secretory responses to hypoglycemia. The mechanism of this defect may be related to autonomic neuropathy. Patients with IDDM who have combined glucagon and epinephrine deficiencies have a 25-fold increased risk of severe hypoglycemia during intensive therapy.
- Sensitive, reproducible, and noninvasive methods that selectively assess parasympathetic and sympathetic nervous system activity have been developed. Studies to date indicate that autonomic nervous system function is abnormal early in the disease and that reproducible measures are available for clinical trials.
- Symmetric distal sensory polyneuropathy is the most studied neuropathic complication in experimental animals. Functional deficits such as impaired motor nerve conduction velocity occur early in both chemically induced and spontaneously diabetic models. At an early stage of diabetes, this conduction defect, as well as nodal electrophysiological impairments, can be reversed by treatment with insulin, sorbinil (an inhibitor of the polyol pathway of glucose metabolism), and myoinositol, although similar treatment in longstanding diabetes has no beneficial effect.
- Electromicroscopic studies in several models of diabetes have demonstrated decreased densities of intramembranous particles in longstanding diabetes. These findings parallel the loss of glial-axonal junctional complexes of the myelin loops, which may be of significance in the distribution of nodal ionophores.
- The isolation and characterization of the ACTH-releasing hormone and the presumptive growth hormone-releasing factor will allow more research into the role of cortisol and growth hormone secretion in carbohydrate and lipid metabolism.
- Positron emission tomography and nuclear magnetic resonance have been used to demonstrate glucose metabolism in various regions of the brain and regional changes in response to various stimuli and neurological diseases.

Future Directions

Based on the biochemical defects that have been elucidated, we are now in a position to evaluate therapeutic modalities for neurological conditions. At the same time, a great deal more research is needed to understand the basic functions of neurological tissues.

- Additional studies are urgently needed to establish the relationship between elevated blood glucose and neuropathy.
- New or improved methods for sensory testing and autonomic nervous system testing should be encouraged. Contractual mechanisms or small business innovation funds could be used for this purpose. Emphasis should be placed on developing and improving simple, reliable devices for use in animals and humans.
- Structure and function studies of human diabetic neuropathy are now feasible and should be encouraged early in the course of the disease. Repeated sampling of peripheral nerves has been demonstrated to be feasible, but maximum information should be derived from each biopsy.
- Epidemiological and longitudinal studies of diabetic neuropathy should be continued and encouraged.
- Tests of patentable drugs should be encouraged from industry. Tests of nonpatentable approaches should be supported by Government and private agencies.
- The potential contribution of the peptidergic nervous system to autonomic and central dysfunction needs to be delineated.
- The use of animal models for diabetic neuropathy should be encouraged. Specific metabolic and biochemical hypotheses should now be rigorously tested. Long-term studies, including the evaluation of new therapies, are particularly needed. Studies in larger animals should be encouraged.

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- The control of appetite by the brain remains one of the most important challenges, since NIDDM is associated with obesity in about 80 percent of the cases. Identification of the neural pathways and neuropeptides involved in appetite regulation could provide an important clue to the prevention of NIDDM.
- Further studies of the roles of insulin and glucose in both central and peripheral nervous system metabolism are needed. Utilization of positron emission tomography and nuclear magnetic resonance in studies of diabetes is a promising area for future research.
- Larger clinical trials of aldose reductase inhibitors and metabolic control are needed to determine if these factors will prevent or reduce the neurological complications of diabetes.

PREGNANCY AND FETAL DEVELOPMENT

Infants born to diabetic mothers have a significantly increased risk of morbidity and mortality. Common problems include respiratory distress, stillbirth, hypoglycemia, prematurity, excessive weight and size, and jaundice. In addition, these infants have a two- to fourfold excess risk for congenital malformations. Scientific advances in recent years, coupled with improved technology and clinical care, have dramatically increased our ability to limit the frequency and severity of the complications of pregnancy (except for the congenital malformations). Many pregnant women also develop a transient abnormality of carbohydrate metabolism called gestational diabetes. Such women have an increased risk of developing diabetes in later life.

Accomplishments

- Several studies have clearly demonstrated that meticulous control of blood glucose and intensive monitoring of the fetus during the second and third trimester of pregnancy can reduce the typical complications of the diabetic pregnancy, except for congenital malformations, to levels approaching those found in nondiabetic pregnancies. These advances apply equally to pregnancies associated with IDDM, NIDDM, and gestational diabetes.
- A preliminary study has provided evidence that meticulous control of diabetes prior to and during the first trimester of pregnancy can reduce the congenital malformation rate.
- As a result of advances in the management of diabetic pregnancies, clinical guidelines were included in *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners*, published by the Board.
- Remarkable scientific advances have been made in several areas directly applicable to the problem of congenital malformations in infants of diabetic mothers. These advances in genetics (recombinant DNA and DNA probes), laboratory techniques in hormone assays, immunology, utilization of stable isotopes, and embryology provide new opportunities to understand and possibly alter the factors responsible for or associated with congenital malformations.

Future Directions

Between 6 and 12 percent of diabetic pregnancies result in malformed infants. This is a tragedy for the infant, the family, and for society. Additional research is needed to better understand and alter the causes of this major complication of diabetes.

- The NICHD collaborative project on diabetes in early pregnancy should be continued until definitive information on the relationship between metabolic abnormalities and congenital malformations is obtained.
- More effective methods need to be developed to educate diabetic women about the advantages of prepregnancy planning and improved control and to screen all pregnant women for gestational diabetes. It is essential that health professionals, especially obstetricians, pediatricians, internists, and family practitioners, give greater attention to and participate in such screening and education programs to bring the current clinical advances to a greater number of women and infants.
- Opportunities for interdisciplinary, collaborative research activities between relevant disciplines must be expanded. These disciplines include internal medicine, pediatrics, perinatology, obstetrics, genetics, molecular biology, mammalian embryology, teratology, and epidemiology.
- Carefully designed studies are needed to focus on potential teratogenic mechanisms, including hyperglycemia, hypoglycemia, and related metabolic abnormalities, during the early (organogenesis) period of pregnancy.
- Additional data should be obtained on the increased sensitivity to insulin hypoglycemia in early pregnancy.

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- More thorough studies are needed on genetic factors in the development of congenital anomalies in diabetic pregnancies, including particular HLA types and family histories of malformations.
- Future studies should address early growth of the conceptus in pregnancies complicated by diabetes, including the incidence of spontaneous abortion.
- Additional studies are needed in mammalian embryology, including more complete detailed descriptions of normal development.
- Studies using *in vitro* fertilization procedures as well as diabetic models in nonhuman primates are needed to obtain information about embryo development in different environments.

BEHAVIORAL AND PSYCHOSOCIAL ISSUES

Physicians and other health care professionals increasingly recognize that behavioral and psychosocial issues can significantly interfere with the therapy of patients with diabetes. The knowledge required to cope with these issues is seriously inadequate. To address the behavioral aspects of diabetes, a program announcement was released in March 1979 by the National Institute of Arthritis, Metabolism, and Digestive Diseases (now NIADDK); the National Institute of Child Health and Human Development; the National Institute of Mental Health; the National Institute on Aging; and the National Heart, Lung, and Blood Institute. As a result of this announcement, and with additional support of other Federal agencies, an increasing number of behavioral studies and projects are being funded.

Accomplishments

Behavioral research is being conducted in a number of promising areas. These areas include psychosocial factors in the metabolic control of diabetes, the extent of depression in newly diagnosed children, the use of relaxation training to stabilize diabetic control, interventions to increase adherence to therapeutic plans, the effects of social support and stress on the course of diabetes, laboratory investigations of the effects of psychological stress on metabolic state, and neurobehavioral effects of diabetes among children and the elderly. The results of these and other projects will soon be reported.

Future Directions

Current investigations have only begun to touch on important areas of study. Many research areas are still not being adequately addressed. These areas include:

- The effects of intensive management techniques on psychological functioning.
- The effects of behavioral and educational interventions on the success of patients learning about and caring for their disease.
- The neurobehavioral assessment of insulin-dependent and noninsulin-dependent children and adults to evaluate the effects of such phenomena as recurrent hypoglycemia.
- Innovative approaches to caring for the elderly, for adults living alone, and for minority populations.
- The development of improved educational approaches for patients with psychosocial problems and low reading ability.
- The effects of family and individual coping on the control of metabolic status and on long-term medical and psychosocial outcomes.
- The impact of a variety of treatments on behavioral outcomes, based on a thorough understanding of the medical and behavioral tasks and challenges imposed by diabetes.

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4. MAJOR CENTERS AND RESEARCH PROGRAMS

The problems presented by diabetes frequently require the combined skills of many disciplines and specialties in biomedical science, education, and health care. The effective integration of these varied resources is most often found in the multidisciplinary centers, specialized research facilities, major research programs, and cooperative clinical trials supported by components of the National Institutes of Health. Answers to many important scientific and clinical problems have resulted from the unique ability of these programs to:

- Facilitate interdisciplinary collaboration.
- Provide shared research resources.
- Stimulate research through pilot and feasibility studies.
- Attract additional scientific disciplines into diabetes research and treatment.
- Improve the training of diabetes health care providers.
- Develop effective collaboration with other Federal, state, local, and private organizations.

These programs continue to serve the national diabetes program extremely well through their contributions to biomedical research, professional education, and patient care.

DIABETES RESEARCH CENTERS

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases funds two types of diabetes-related centers: Diabetes Endocrinology Research Centers (DERC) and Diabetes Research and Training Centers (DRTC). These centers are located at institutions that already have high-quality programs in basic and clinical research related to diabetes and its complications. The DERC's are devoted exclusively to biomedical research while the DRTC's have the additional responsibility to improve the transfer of research advances through Model Demonstration Units (MDU) and other programs to train health professionals in modern diabetes treatment practices.

Each center represents a cooperative, multidisciplinary approach to diabetes issues and provides an environment for interaction between basic and clinical investigators. Cooperative projects are encouraged through the provision of core facilities (shared resources) and support for new initiatives (pilot and feasibility studies). In the DTRC's, this interaction also encompasses health care professionals interested in training and information transfer activities.

Five DERC's operated in fiscal year 1983 at a combined support level of $3.2 million. Total support for the seven DRTC's was $9.5 million in fiscal year 1983. Program guidelines require that each center allocates 50 to 75 percent of its grant budget to biomedical research activities. The balance is used for the training and information component. The current DERC's and DRTC's are shown in table 2.

Expansion of research, both in total amount and in the percentage of multidisciplinary activities, has been successfully accomplished within the host institutions of the centers. This expansion is a direct result of several advantages offered by a center: (1) additional faculty and facilities, primarily as a result of increased commitment from host institutions; (2) contributions of established investigators in other areas using their expertise in diabetes-related research; (3) support of pilot and feasibility studies, particularly for new investigators; and (4) services, consultation, and training available from the shared resources. Many of the important advances detailed in the research section of this report were made at institutions that have diabetes centers.

Shared resources are an important ingredient in the research efforts at the diabetes centers. These resources contribute to increased productivity through:

- Greater collaboration.
- Attraction of new and established investigators from related fields into diabetes research.
- Availability of expensive equipment and more efficient use of all equipment.

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Table 2

DIABETES ENDOCRINOLOGY RESEARCH CENTERS

Baylor College of Medicine Houston, Texas	University of Pennsylvania Philadelphia, Pennsylvania
University of Iowa Iowa City, Iowa	University of Washington Seattle, Washington
University of Massachusetts Worcester, Massachusetts	

DIABETES RESEARCH AND TRAINING CENTERS

Albert Einstein School of Medicine New York, New York	Vanderbilt University Nashville, Tennessee
University of Chicago Chicago, Illinois	University of Virginia Charlottesville, Virginia
Indiana University Indianapolis, Indiana	Washington University St. Louis, Missouri
University of Michigan Ann Arbor, Michigan	

- Flexibility to pursue limited developmental research to ensure that the latest, best, and most-needed clinical services are available.
- Enhancement of clinical research.
- Availability of added consultation and training.
- Greater institutional support.
- Lower costs through bulk purchasing, sharing of facilities, quality control, greater volume of service, and a center mechanism to screen requests, monitor usage, and prioritize needs.

An important feature of all centers is the support of short-term pilot and feasibility studies. Of 160 completed studies, 44 percent of the investigators were subsequently awarded NIH grants on closely related subjects, and 17 percent received similar funding from other sources. These results are impressive.

As stated earlier, each DRTC has developed a Model Demonstration Unit (MDU) to facilitate the training of health professionals in the treatment and education of diabetic patients. As the centers have matured, the MDU's have also provided a number of unique advantages for the promotion of clinical research:

- An environment separate from general clinics.
- A patient data system with reasonably well characterized patient information.
- Enhanced opportunity for collaboration with basic biomedical scientists.
- The possibility of initial funding for pilot and feasibility studies.
- Services and consultation from the shared biomedical resources.

Needless to say, these MDU's meet an additional urgent need by providing an opportunity to attract physicians into a career in research.

The DRTC's have developed a wide variety of materials for the education of both health professionals and patients. The majority of these materials have been evaluated in local settings, and a significant number have been applied outside the centers. Manuals, curricula, and other similar materials also are deposited with the National Diabetes Information Clearinghouse (NDIC). NDIC is preparing a compendium that will include listings of all materials available from the DRTC's and other major sources.

As directed by the original legislation for this program, the DRTC's are assisting national, state, and local diabetes projects. Recent activities include (1) collaboration with the National Diabetes Control Program of the Centers for Disease Control and the Model Diabetes Care Program of the Indian Health Service; (2) consultation to the Diabetes Control and Complications Trial sponsored by NIH; and (3) assistance to the National Diabetes Advisory Board on projects related to professional and patient education. Thus the DRTC's are fulfilling their role as national resources for the diabetes program.

The diabetes centers are evaluated on a continuing basis by both internal and external organizations, which includes the NIH peer review system, the Board, NIADDK staff, and individual center-based in-house studies. These reviews support continuing and strengthening the diabetes centers program.

DIABETES CONTROL AND COMPLICATIONS TRIAL

One of the most critical clinical issues in diabetes mellitus concerns the relationship between metabolic control and the chronic complications of the dis-

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ease. Debate on this issue has centered largely on two interrelated issues: (1) whether, or to what extent, the chronic complications of diabetes are related to the metabolic derangements that characterize the disease and (2) if so, what degree of metabolic control is necessary to prevent the development or ameliorate the progression of such complications.

In its report to Congress in 1975, the National Commission on Diabetes recommended a clinical study to assess the effect of treatment of Type I diabetes on the development of microvascular and macrovascular complications. Extensive discussions between NIH and the diabetes community led to a consensus that such a study is ethical and desirable. Acting upon this consensus, NIADDK initiated a multicenter collaborative clinical trial—the Diabetes Control and Complications Trial (DCCT)—consisting of the following four phases:

- Phase I: Planning (1 year)
- Phase II: Feasibility Study (2 years)
- Phase III: Full-Scale Clinical Trial (7 to 10 years)
- Phase IV: Data Analysis and Reporting (1 year)

Twenty-one clinical centers and a coordinating center were selected to participate in the study on the basis of scientific peer review. Phase I, initiated in March 1982 to develop the phase II study protocol, was completed in February 1983. Phase II was initiated on August 1, 1983. The objectives of phase II include:

- Determination of whether a statistically significant difference in the level of blood glucose control can be achieved between the standard and experimental therapy groups.
- Determination of the relative efficacy, utility, patient acceptability, and safety of an experimental and a standard therapy for Type I diabetes.
- Determination of whether specific metabolic parameters and defined retinal, vascular, and neurological endpoints can be measured and documented with acceptable precision and accuracy.

A total of 252 patients between 13 and 39 years old are being studied in phase II. Patients have been assigned randomly to either the conventional or experimental therapy group. Conventional therapy consists of not more than two daily injections of insulin and an individualized dietary program. The experimental treatment group receives intensive insulin therapy and additional reinforcement of the dietary program. All participants will undergo a set of regularly scheduled followup procedures, and study data will be analyzed at periodic intervals. Blood glucose measurements will be used as the primary indicator of overall metabolic control. Diabetic retinopathy will be the primary endpoint because it is an early indicator of disease progression that may be affected by blood glucose control. Neurological measurements also are being studied. If warranted by the results of the feasibility study, a 7- to 10-year full-scale trial will be undertaken.

Mechanisms have been established for assuring quality control and for monitoring the performance of all study components on a regular basis. In addition, two independent advisory groups will report directly to NIADDK. The Data, Safety, and Quality Review Group (DSQ) will monitor the study as it proceeds for data quality and patient safety. Based on analyses and observations by the DSQ, the Policy Advisory Group will assess the feasibility of initiating the full-scale trial and submit a recommendation to NIADDK in mid-1985. These two groups, composed of representatives of the diabetes community and experts in the methodological, operational, medical, neurobehavioral, ethical, and biostatistical aspects of clinical trials, also reviewed and approved the study protocol.

Although the DCCT is primarily an NIADDK initiative, the National Eye Institute, the National Institute of Neurological and Communicative Disorders and Stroke, the National Heart, Lung, and Blood Institute, and the Division of Research Resources are collaborating with NIADDK in the initial phases of the trial. NIADDK also has received donations of supplies, equipment, and services for the DCCT from various commercial firms. This collaboration provides a model for productive interaction between the public and private sectors in committing the resources necessary to initiate this long-awaited study. The Board commends the participating organizations for their cosponsorship and active support of the DCCT and endorses the phased approach to the conduct of the trial.

CLINICAL TRIALS ON EYE COMPLICATIONS OF DIABETES

One of the most common complications of diabetes is diabetic retinopathy, a disease of the retina, the light-sensitive tissue that lines the inside of the eye. As the duration of diabetes increases, retinopathy affects an increasing percentage of patients. After 15 years of diabetes, more than 50 percent of patients have retinopathy, with impairment of vision in 10 to 20 percent and legal blindness in 5 to 10 percent.

The ophthalmologist's ability to prevent severe visual loss in people with diabetic retinopathy has improved dramatically in the past decade, thanks to

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photocoagulation, a treatment in which powerful beams of light from a laser are directed into the eye and used to destroy diseased retinal tissue. The value of photocoagulation was conclusively demonstrated in the NEI-sponsored Diabetic Retinopathy Study, which proved that laser treatment could reduce the risk of severe visual loss by 60 percent in people with advanced or moderately advanced diabetic retinopathy. NEI subsequently began a campaign to inform primary care physicians, eye care specialists, and the public about the results of this study, thereby encouraging timely and appropriate use of photocoagulation in patients who are at risk of losing their vision.

The successful completion of the Diabetic Retinopathy Study has served as an invaluable background for the four clinical trials that are currently under way to evaluate various medical or surgical interventions designed to either treat or prevent diabetic retinopathy.

The Early Treatment Diabetic Retinopathy Study (ETDRS), begun in fiscal year 1981, has recruited approximately 3,000 patients and should achieve the originally planned sample size of 4,000. A primary objective of the ETDRS is to determine whether treatment of earlier stages of diabetic retinopathy by aspirin, by prompt photocoagulation, or by both combined is more effective in preserving vision when compared to photocoagulation that is deferred until high-risk proliferative retinopathy develops. If earlier treatment with photocoagulation proves to be more effective, practitioners may apply laser treatment to patients with moderately severe retinopathy who would not currently be considered for treatment. On the other hand, if neither aspirin therapy nor early laser treatment is found to be advisable, ophthalmologists will know to limit the use of photocoagulation to those patients whose diabetic retinopathy has progressed to a fairly advanced stage and to look to future research for a better means of early treatment.

Ideally, the best treatment would be therapy that prevents the onset of diabetic retinopathy. Promise in this regard comes from laboratory research that has demonstrated in animals the benefits of aldose reductase inhibitor drugs in retinopathy. The Sorbinil Retinopathy Trial, a randomized study of more than 700 diabetic patients with early or no retinopathy, has been initiated to evaluate the safety and efficacy of sorbinil, an aldose reductase inhibitor. Changes in retinopathy, sensory thresholds, nerve conduction velocities, and signs or symptoms of neuropathy will be assessed. The trial will be funded by a pharmaceutical firm. NEI will oversee the policy, data, and safety monitoring of the study.

NEI is continuing to support another multicenter clinical trial, the Diabetic Retinopathy Vitrectomy Study (DRVS), to find the optimal time for undertaking the vitrectomy operation, in which blood-clouded vitreous and scar tissue caused by diabetic retinopathy are removed. The DRVS has completed recruitment, with a total of 997 cases randomized to either early vitrectomy or conventional therapy (i.e., vitrectomy at a later date if vitreous hemorrhage fails to clear or retinal detachment develops). Followup should be completed by mid-1985, and the results of this study should provide practical clinical information for determining when to perform vitrectomy for severe diabetic retinopathy.

NEI also is participating in the NIADDK-directed Diabetes Control and Complications Trial described earlier. Diabetic retinopathy will be the primary endpoint in this study.

MAJOR RESEARCH PROGRAMS IN PREGNANCY AND INFANTS OF DIABETIC MOTHERS

Because the incidence of congenital defects in diabetic pregnancies is two to four times greater than that in nondiabetic pregnancies, the National Institute of Child Health and Human Development (NICHD) initiated the Diabetes in Early Pregnancy Project in 1981. This collaborative project is designed to ascertain whether careful control of diabetes during the first trimester of pregnancy can reduce the risk of birth defects and to discover the mechanisms by which such defects arise. The project involves scientists at five university hospital centers.

Enrollment of women began in January 1981. By the end of November 1983, 715 diabetic women and 843 nondiabetic women had been enrolled. Women who become pregnant are monitored carefully during the first 12 weeks of pregnancy, the period of organogenesis. This monitoring includes daily assessment of blood and urine glucose as well as weekly hospital visits. The offspring of all pregnancies are carefully screened for external as well as internal congenital defects. So far, 213 diabetic women and 230 control women have given birth. Preliminary analysis of the data is now under way.

Many other aspects of diabetic pregnancies are being addressed by NICHD's Perinatal Emphasis Research Centers. The impetus behind the formation of these centers is Senate Report No. 94-366, which directed NICHD "to undertake concerted biomedical and behavioral research efforts directed toward infant survival." In carrying out this congressional directive, NICHD mounted a major research effort in the area of diabetic pregnancies, since the outcomes of these high-risk pregnancies contribute significantly to the overall rates of infant mortality and morbidity. Four of the seven centers focus on diabetic pregnancies: Brown University, Case-Western Reserve University, Northwestern University, and the University of New Mexico. In

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fiscal year 1983, diabetes-related research at these four sites was funded at a level of $2.3 million.

A central goal of the center at Case-Western Reserve University is to assess the effects of rigid metabolic regulation of diabetes during pregnancy on the mother and her newborn. It has been learned that energy metabolism in well-controlled diabetic pregnancies does not differ from that of nondiabetic pregnancies. Pregnant diabetic subjects are currently entering a clinical trial designed to assess the effects of insulin pump therapy versus conventional insulin therapy on maternal metabolism and pregnancy outcome.

The center at the University of New Mexico supports basic studies of islet cells, hormone metabolism, and fetal development. Research also is continuing on the development of an implantable miniature pump and insulin reservoir regulated by an external microelectronic control system. Prototype models currently are being implanted in diabetic dogs.

A major aim of the center at Brown University is to evaluate hormonal and fuel metabolism in diabetes during pregnancy. Studies are progressing on the rates of gluconeogenesis from specific precursors in pregnant diabetic and nondiabetic women as well as in their offspring. Studies are also progressing on hyperinsulinemic rhesus monkey models of macrosomia and on a fetal sheep model of hyperinsulinemia. Preliminary behavioral data on rhesus monkeys made hypoglycemic at birth following fetal hyperinsulinemia suggest long-term effects of prolonged symptomatic neonatal hypoglycemia on both emotional behavior and complex cognitive functions.

At the Northwestern University center, careful measurements of metabolic fuel consumption, hormonal concentrations, and diabetic control have now been performed on a series of several hundred diabetic women during pregnancy. Outcome data on these tightly controlled diabetic pregnancies indicate a low incidence of perinatal mortality.

PERIPHERAL NEUROPATHY CLINICAL RESEARCH CENTER

Peripheral nerves provide the vital link between the central nervous system and the muscles, skin, blood vessels, and all other organs. While some degree of impaired peripheral nerve function (neuropathy) occurs in almost all patients with longstanding diabetes, disabling neuropathy may develop in up to 25 percent of diabetic patients. This condition may predispose diabetic patients to ulceration of the toes and feet and ultimately to amputation, severe muscle pain, impaired function of the bowels, and impotency in males.

To expand critically needed research in this area, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) supports several investigator-initiated research projects, as well as a peripheral neuropathy research center at the Mayo clinic in Rochester, Minnesota. The research center conducts a multidisciplinary program that includes the following projects related to diabetes:

- Development of standardized procedures to quantitate nerve function and to provide computerized neuropathic disability scores based on physical examinations, neurological evaluations, and studies of biopsied nerve segments from diabetic and control population samples.
- A clinical trial using insulin infusion pumps to evaluate the effect of better blood glucose control on diabetic neuropathy.
- Use of morphologic, electrophysiologic, immunologic, and biochemical approaches to understanding the cause of peripheral neuropathy.

GENERAL CLINICAL RESEARCH CENTERS

The General Clinical Research Center (GCRC) program, funded by the NIH Division of Research Resources (DRR), supports noncategorical clinical research facilities at academic institutions. The GCRC's provide a unique environment for controlled investigation because they are discrete units with their own beds, nurses, dietitians, and other support staff. Research protocols related to a variety of diseases compete on the basis of scientific merit for the use of the facilities. It is noteworthy that 3,939 investigators supported by NIH grants conduct 3,460 projects in these centers. This high degree of involvement attests to the quality and importance of the GCRC's not only to diabetes but also for the entire spectrum of health problems. The vast majority of all clinical investigation related to diabetes, including activities of the DRTC's, DERC's, clinical trials, and other diabetes research programs described earlier, is conducted in these facilities. Many of the major research advances directly applicable to the management of diabetes and its complications are the result of research conducted in GCRC's.

The GCRC's also contribute to the training of urgently needed physician-scientists. Of the 140

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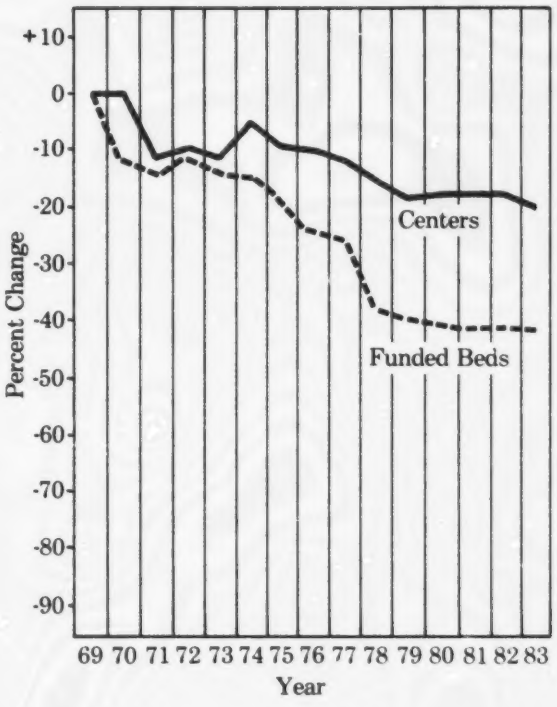
clinical investigators who have received support through the Clinical Associate Program since 1975, 17 percent have chosen to pursue diabetes-related projects. In addition, fellows, residents, interns, medical students, and paraprofessionals such as nurses and dietitians receive research training in the GCRC's.

The budget for this important program has not kept pace with inflation over the past 15 years. Although the program received moderate increases in the last 2 years, the current budget, measured in constant dollars, is still 16 percent below 1969. This situation has led to a 20-percent reduction in the number of centers, from 93 to 74, and a 42-percent reduction in the number of beds, from 1,023 to 595 (figure 1). It should be noted, however, that outpatient visits have increased during this period from 1,175 to 106, 327 a year. The serious decline in program resources may be directly related to the noncategorical nature of the program, since specific disease constituencies have not felt the need to focus attention on this unique activity. However, it should be clearly recognized that a further decline in resources would have serious, negative implications for clinical research across a broad spectrum of health problems. To correct this serious decline in an essential research resource, the Board's budget recommendations for fiscal year 1985 (table 1) include a total funding level of $90 million for the GCRC program, an increase of $8.1 million over the 1984 level.

Figure 1

PERCENT CHANGE IN NUMBER OF GENERAL CLINICAL RESEARCH CENTERS AND NUMBER OF BEDS



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5. RESEARCH MANPOWER

The increasingly critical problem of an inadequate supply of new, young investigators for research in diabetes has been emphasized in the previous reports of the National Diabetes Advisory Board. This situation is especially acute for physician-investigators but is also applicable to Ph.D. investigators. Although both types of investigators have made important contributions to the exciting research progress detailed earlier in this report, the physician-scientist is uniquely capable of conducting clinical research because of the nature of his or her training.

NATIONAL RESEARCH SERVICE AWARDS (NRSA)

Previous reports of the Board indicated that a minimum of 300 postdoctoral fellows must begin research training each year to maintain the current number of investigators involved in diabetes-related research. This minimum number would not permit the expansion necessary to exploit fully the research opportunities that hold promise for preventing the complications of diabetes and hopefully for curing this disease. Although NIH awards both individual fellowships and institutional training grants to provide research training to individuals selecting a research career, the actual number of young individuals entering research training has steadily decreased. For example, the number of individual fellowships related to diabetes research decreased from 66 in 1978 to 35 in 1983, and the number of persons receiving research training through institutional training grants fell from 183 in 1980 to 156 in 1983. The total number of trainees is, therefore, less than two-thirds of the number necessary to maintain the current level of investigators.

In addition to problems at the trainee level, there is a serious problem in maintaining a core of well-trained research scientists and research physicians at the senior level. This is illustrated by the fact that the average duration of a senior scientist as the principal investigator on a research grant is fewer than 7 years. This is the result of many factors. In some cases, senior physician-scientists move into administrative positions, decreasing their availability for active research. In other cases, the overly competitive grant situation strikes at the security of established investigators by undermining their research support. If the investigators are physicians, they may be forced to spend more time in health care delivery than in research. Basic scientists may turn to increased teaching responsibility. In both cases, once this change occurs, the senior scientists are unlikely to return to the active research pool, removing all of the skills and experience they have gained.

RESEARCH NEEDS

The magnitude of these problems became more apparent as a result of the deliberations of the 12 workgroups at the Second National Diabetes Research Conference sponsored by the Board in September 1983. Many of the most exciting and promising areas of research involve disciplines such as immunology and molecular biology, which traditionally have not been identified with diabetes research. If these opportunities are to be exploited fully, a significant increase in the number of investigators with expertise both in these areas and in diabetes is urgently needed.

While it is difficult to assign specific numbers to these needs, a projection of two new investigators with training in immunology and molecular biology for half of all the medical schools in the United States would require approximately 125 individuals. This is also true for the disciplines of genetics, virology, and especially epidemiology. The workgroup concerned with the etiology of Type I diabetes conservatively estimated an immediate need for 40 new epidemiologists knowledgeable about diabetes. The islet cell transplantation workgroup could identify fewer than 25 major investigators in this crucial subject throughout the world. This area of research, which has the potential for curing Type I diabetes, needs an additional 40 to 60 new investigators. Similar shortages were iden-

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tified in many other areas of diabetes research, especially those concerned with the chronic complications of the disease. For example, there are fewer than 15 laboratories actively involved in research in diabetic neuropathy. All of these special needs are in addition to the 300 trainees previously identified by the Board as necessary to maintain the current diabetes research effort.

DISINCENTIVES FOR RESEARCH TRAINING

As a consequence of the decreasing research manpower in diabetes, many medical schools are actively but unsuccessfully seeking young investigators in this area. Although the Board has previously delineated the disincentives that contribute to this serious situation, little or no action has been taken to eliminate them. In fact, in some areas, the disincentives have become even greater. Probably the greatest impediment to an individual seeking training for a career in research is the decreasing Federal support for biomedical research in general and the low level of funding for investigator-initiated research. Students are quite aware of their teachers' difficulties in continuing their research careers because of reductions in the percent of scientifically meritorious research grants that are funded and because of further reductions in the budgets of awarded grants below previously committed levels. This uncertain future discourages individuals from selecting a research career since they may not receive funding for their research project. This uncertain future is a particular disincentive to physicians who have the option to enter the private practice of medicine with its greater security and financial rewards compared to academic medicine. However, the marketplace also is making significant inroads on Ph.D.-trained investigators in diabetes-related basic science disciplines such as biochemistry and molecular biology.

Another significant impediment to embarking on a research career is the noncompetitive level of fellowship stipends. Although the stipend was increased 5 percent in FY 1983, this was the first increase since 1980. The stipend is about 20 percent less than the average salary that a resident with the same number of years of experience would receive in a U.S. teaching hospital. The problem is especially acute for physicians with 2 or 3 years of clinical training prior to entering a research training program. At this point in their career, physicians can choose to enter private practice with a significantly greater income, while the research training stipend will actually be less than their previous income as a resident. Because of the high cost of medical education, most physician graduates have significant indebtedness, which they cannot repay on the low stipend that they would receive for research training.

Finally, current Government regulations stipulate that NRSA trainees must reimburse the Government for the stipend beyond the first year of training if they do not continue in a research or teaching career. This disincentive is particularly difficult for physicians. Since they have had no research training during medical school, they may not know whether they have the capability for a successful career in research. Only by doing research can an individual determine whether this would be an appropriate career choice. The payback provision discourages individuals who might be interested in research but have never had the opportunity to try it.

RESEARCH CAREER TRAINING PROGRAMS

Many of the problems described above have been recognized by NIH, which has instituted programs designed to increase research manpower in general. For example, NIH has developed a program that will support short-term (3 months) research experiences for medical students during their summer vacations. It is believed that the earlier individuals are exposed to research the more likely they are to choose research as a career.

A variety of research career awards have been established by Institutes of NIH to support young investigators during the crucial period between the end of their research training and their establishment as independent investigators. The Clinical Investigator Award, the new Physician-Scientist Award, and the Clinical Associate Physician Award of the General Clinical Research Centers Program are designed specifically for physicians. The Research Career Development Award makes no distinction between M.D.'s and Ph.D.'s.

The Physician-Scientist Award is intended to provide the opportunity for clinically trained individuals to develop the research skills needed to become independent biomedical investigators. The awards are structured to provide clinicians with up to 5 years of didactic study and laboratory experience under a sponsor with extensive experience in basic science. Both individual and institutional awards are available.

Unfortunately, the total number of all diabetes-related research career awards decreased from 63 in 1980 to 50 in 1983, reflecting both the overall decline in the number of individuals entering the earlier stages of the training process and the decrease in available research dollars. Therefore, the conclusion and recommendations in the Board's last report, repeated below, are even more imperative now since the problems they address have increased.

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RECOMMENDATIONS

The Administration's proposed fiscal year 1985 budget would result in a significant reduction in the number of fellowships and career development awards at a time of increasing need and opportunity. For example, the proposed budget for NIADDK includes a reduction of 77 fellowships and 15 career development awards. Therefore, the following recommendations require immediate attention:

- The total number of diabetes-related fellowships (individuals plus those on training grants) should be increased to a minimum of 300 per year.
- Efforts should be made to expand the applicant pool for research career development awards. The most important step in this regard will be an increase in funds available to support approved investigator-initiated research applications.
- Federal training stipends should be made competitive with salaries for residency training programs of teaching hospitals and adjusted annually to compensate for increases in the cost of living.
- The stipend payback provision should be removed.
- Support for individual research grants should be stabilized to provide the incentive for potential clinical and basic scientists not only to enter and complete research training but to remain in active investigative careers. New mechanisms to provide long-term support for established investigators should be considered.

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6. NATIONAL DIABETES CONTROL PROGRAM OF THE CENTERS FOR DISEASE CONTROL

The overall goal of the National Diabetes Control Program is to reduce morbidity, mortality, and cost burdens resulting from the preventable complications of diabetes. While major advances have been achieved in the ability to treat diabetes and to prevent or reduce the severity of some of its complications, the effective dissemination and application of these advances at the community level depend on a diverse health care system with many internal barriers to this goal. Therefore, the National Plan to Combat Diabetes, developed by the National Commission on Diabetes in 1975, recommended that concerted action be taken to overcome these barriers at the national, state, and local levels. The Centers for Disease Control (CDC) was assigned the major responsibility in this area because of its traditional role in public health and disease control and its established relationships with state and local health departments.

CDC subsequently established diabetes control projects in 20 states (figure 2). The basic approach of CDC and these states has been to (1) conduct special studies and demonstration projects to identify strategies for addressing the public health problem of diabetes and (2) establish mechanisms for rapidly translating proven control strategies into community practices to improve patient outcome.

The special studies conducted within this program focus on the epidemiologic description of factors contributing to or causing excess diabetes morbidity, mortality, and associated costs. The interventions are designed to remove or reduce those factors in defined populations or care settings. The project states are currently conducting more than 60 special studies and interventions. Significant and positive outcomes have already resulted, as described below.

REDUCTION OF HOSPITALIZATION THROUGH DIABETES PATIENT EDUCATION

Persons with diabetes are expected to assume a major share of responsibility for their own care. Only an informed person can carry out this responsibility effectively. Evidence is growing that inadequate patient knowledge results in multiple hospital admissions, excessive use of emergency rooms, a higher incidence of both acute and chronic complications, and an increase in the economic and social burden of this disease. Many project states have developed special interventions to assess the impact of carefully designed diabetes patient education programs. These interventions have documented significant reductions in hospitalizations and associated costs. The savings are significantly greater than the costs of the interventions. Several examples include the following:

- The final report on the Reimbursement Pilot Study for the Maine Ambulatory Diabetic Education and Followup Program, submitted to Maine Blue Cross/Blue Shield in November 1983, documented a 39.8-percent reduction in the number of diabetics hospitalized, a net reduction of 32.2 percent in the number of hospital days, and a savings of $359,835 in hospitalization costs for the 813 patients. This represents a net savings of $237,885 or $293 per patient after accounting for the cost of the education program. Based on these findings, the Board of Directors of Maine Blue Cross/Blue Shield made reimbursement for diabetes outpatient education a permanent benefit for Blue Cross/Blue Shield members. Similar coverage has been provided in Maine by Medicare, Medicaid, and a private insurance company.

- The Michigan Diabetes Control Program, in cooperation with the Saginaw County Health Department, established a program of home visits to help recently hospitalized diabetic patients with the management of their disease. Preliminary analysis of results from the 73 participants showed a 43-percent reduction in the total number of hospital admissions (from 147 in the year prior to the program to 84 in the following year) and a reduction in the average length of stay from 9.4 to 8.7 days.

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When diabetes was the primary diagnosis, hospital admissions within the same group decreased from 76 to 25.

- In Rhode Island, outpatient education classes were conducted for 193 persons with insulin-dependent diabetes mellitus. The program emphasized improvement of diabetes self-management. Health care utilization comparisons at 12 months pre- and post-course showed a 58-percent reduction in hospital admissions for preventable complications of diabetes (defined in the study as DKA, hypoglycemia, hyperglycemia, and infection). Total persons requiring hospitalization decreased by 48 percent, and days of hospitalization decreased 41 percent.

PROGRESS IN THIRD-PARTY REIMBURSEMENT FOR NECESSARY DIABETES SERVICES

In addition to the Maine example cited above, other states have reported that reimbursement agreements for essential diabetes-related services have been reached with or are being seriously considered by Blue Cross/Blue Shield, Medicare, Medicaid, and other agencies. Progress in this area reflects a growing awareness and acceptance of the results reported by the national diabetes control program and the project states as described in the following examples:

- Michigan's Task Force on Third-Party Reimbursement has achieved Medicare reimbursement for diabetes education in hospital outpatient settings. This reimbursement has been obtained on a statewide, nondemonstration basis.

- Reimbursement for diabetes outpatient education demonstration programs has been authorized by Medicare, Blue Cross/Blue Shield, and other third-party payors in New York, Colorado, Ohio, Illinois, and California.

- As a direct result of the Maine study above, several states have received grants from Blue Cross/Blue Shield to study the effectiveness of diabetes outpatient education in their respective areas.

- In many states, reimbursement benefits for insulin infusion pumps and blood monitoring units have been approved by Blue Cross/Blue Shield.

A summary of these advances and related issues has been prepared by CDC staff for publication in a national journal. The article, entitled *Reimbursement Issues in Diabetes: A Review*, outlines approaches taken by states and diabetes control programs in successfully seeking reimbursement for outpatient education by Blue Cross/Blue Shield, other commercial insurance companies, Medicare, and Medicaid.

IMPROVEMENT IN THE QUALITY OF DIABETES PATIENT CARE

Obviously, the reductions in hospitalization through patient education cited above represent a definite improvement in patient care. Quality care also may be achieved through measures other than reduced hospitalization, as shown in the following two typical state projects:

- A project in Colorado identified an excessive rate of diabetes complications in extended care facilities. An analysis of contributing factors led directly to the preparation of *A Guide to the Development or Revision of Nursing Care Policies and Procedures on Diabetes* to assist the administrative staff of extended care facilities in assessing and improving diabetes care.

- A Mississippi project to improve diabetes care has built upon an existing state program. As a result, Mississippi now conducts a comprehensive screening and treatment program for diabetic eye disease in its public health clinics. Patients are examined clinically and with fluorescein angiography. Treatment is provided as indicated by the examination, and patients are tracked and placed into a system for annual reexamination to assure followup and to assess the impact of the intervention. It is hoped that results from this study will demonstrate the feasibility of offering such a service on a statewide basis at low cost.

IMPROVED INTERORGANIZATIONAL NETWORKS

An informal network of organizations and individuals from the private and public sectors has been established at the national level and within each state's project area. Many groups that previously worked in isolation are now part of a broad-based, coordinated effort with common goals. These networks are essential for the effective transfer of project findings and research advances into community practice. CDC also has encouraged cooperative activities with related chronic disease programs and other elements of the broader medical and public health systems. For example, the Association of Schools of Public Health is working with CDC on

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two projects: the Johns Hopkins University is developing strategies to translate effective diabetes control strategies into public health settings, and the University of Washington is assessing the utility of available data sets to develop surveillance systems for chronic diseases.

THE EVOLUTION OF THE NATIONAL PROGRAM

The many accomplishments of this program were not achieved easily. When the national program was initiated in 1977, there was no consensus on the components of an effective public health approach to diabetes. There also was no national consensus on the diagnosis, treatment, and case management of diabetes or on standards for diabetes patient education. Little was known about the sources, types, or limitations of data available at the community level for measuring the magnitude of diabetes-related problems or for assessing the results of interventions. Additional problems identified by the states included inadequate provider knowledge, absence of an integrated provider system, and lack of third-party reimbursement for patient education services.

In the absence of a proven health model, CDC issued a request for proposals to develop and evaluate community-based diabetes control demonstration projects. Ten state health departments were awarded contracts in 1977. Two additional states were added in 1979, and eight more were added in 1980. While these 20 states began to work in their respective areas, CDC initiated efforts at the national level to develop consensus on a variety of issues essential to an effective program. The following documents, developed by CDC or with CDC assistance, reflect essential advances in the national effort to control the public health aspects of diabetes:

- *CDC-State Patient Education and Professional Education Guidelines*
- *Diabetes Program Handbook*
- *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners*
- *National Standards for Diabetes Patient Education Programs*

The *Guide for Primary Care Practitioners* was prepared under the aegis of the National Diabetes Advisory Board as an outgrowth of the 1980 Diabetes Health Services Conference. CDC made a major contribution to the conference by providing morbidity and mortality data from the project states as well as information about barriers to quality patient care that appeared most amenable to intervention. This information was subsequently incorporated into the guide, which also was field-tested in several project states. Following publication by the Board, CDC assumed a major responsibility for the widespread dissemination of the document and implementation of its prevention and treatment strategies. CDC has performed a similar supportive role in the development of the *National Standards for Patient Education Programs*, prepared under the leadership of the Board.

In addition to their direct contribution to the national program, these four documents represent two additional important developments: (1) consensus within the diabetes community in regard to essential components of effective diabetes treatment and control and (2) a focused effort to transfer this consensus to segments of the health care system not familiar with these advances. Each of these documents also has served to trigger additional, complementary initiatives by other organizations to improve the availability of useful and accurate educational materials. Considerable credit must be given to CDC and the state projects for identifying the need for consensus in these areas.

FUTURE PROGRAM OPPORTUNITIES

As the project states have identified effective diabetes control strategies within their demonstration areas, CDC has been able to develop plans for the further evolution of the program from a series of diverse, time-limited projects to a truly national program with the potential for successful prevention and control efforts within larger geographic areas. To achieve this broader goal, CDC officials have developed program guidelines for all states to ensure a common framework for action, a focus on national priorities, and a greater opportunity for collaboration between states, while retaining flexibility for each state to tailor programs to local needs and resources. To the extent that funds are available, each state will:

- Promote patient and professional use of the standards of care contained in the *Guide for Primary Care Practitioners*.
- Encourage, plan, and evaluate diabetes patient and professional education programs according to common criteria.
- Encourage and assist interested parties in assessing their own programs according to these criteria.
- Improve linkages between diabetes and related public health programs, including hypertension, maternal and child health, renal and eye disease, nutrition, and rehabilitation services.

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In addition, project states will place greater emphasis, within available resources, upon several new collaborative activities designed to expand the scientific base of the national program and translate state-of-the-art advances and recommendations into operational guidelines for broader community application. These activities may include:

- Long-term, prospective cohort studies of diabetes and hypertension, diabetes and pregnancy, gestational diabetes, and the use of continuous subcutaneous insulin infusion pumps.
- Development of mechanisms that encourage the application of current clinical information to public health interventions in diabetes, e.g., screening for diabetic retinopathy and establishment of prepregnancy education programs.
- Formal evaluation of the dissemination and impact of the *Guide for Primary Care Practitioners.*
- Pilot implementation of the *National Standards for Diabetes Patient Education Programs* and the associated recognition process.
- Development of a cooperative reporting system for diabetes-related data from selected hospitals.

RECOMMENDATION

The Board has been tremendously impressed with the accomplishments achieved by the CDC program in a short time and with very limited resources. Diabetes patient care is being improved in localities encompassed by the intervention projects, and the cost-effectiveness of many interventions has been recognized by participating health care organizations and insurance carriers. While application of these advances is currently limited to demonstration areas, CDC is establishing methods to share them with interested communities throughout the country.

Unfortunately, the program has been severely constrained by financial and personnel restrictions throughout its history. The program's budget has remained at $5.98 million for the past 3 years despite inflation and increasing opportunities. CDC's leadership has used these limited resources wisely and effectively to generate an impressive level of activity. However, expansion of effort to additional priority activities within the project states, not to mention extension of the program to additional regions of the country, cannot be implemented without additional funding. A minimum increase of $3 million is needed to (1) intensify efforts in the 20 current project states; (2) expand the program to five additional states; and (3) initiate high-priority regional and national projects that will transfer program accomplishments to a wider area and population.

The Board recommends that the Administration and Congress provide $9 million and necessary additional personnel for CDC's National Diabetes Control Program in fiscal year 1985.

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7. MODEL DIABETES CARE PROGRAM OF THE INDIAN HEALTH SERVICE

EXTENT OF THE PROBLEM

Diabetes in American Indians is significantly more severe than in other U.S. populations in terms of prevalence, morbidity, and premature mortality. In several tribes, over 40 percent of the adults are affected with adult onset (Type II) diabetes, compared to approximately 3 percent of the overall U.S. adult population. Insulin-dependent diabetes (Type I) is uncommon among American Indians. Continuing increases in diabetes prevalence and complications have been documented in several tribes, including the Pimas, where the age-sex specific prevalence increased 42 percent between 1967 and 1977. During this interval, obesity also became more common, particularly in persons less than age 35. Studies in various tribes have demonstrated both strong associations between obesity and Type II diabetes and the marked potential for metabolic improvement with weight control. While the exact etiology of the disease and specific genetic-environmental interactions are not yet defined, diabetes specialists have recommended prompt implementation of known effective prevention and treatment strategies to reduce the excessive morbidity and mortality from diabetes in Indian communities today.

Major complications of diabetes are increasing in frequency among American Indians and include renal failure, amputations, and blindness. Diabetes has become the second leading reason for adult outpatient visits in the Indian Health Service. Costs for managing the disease and its complications are increasing, and as diabetes prevalence increases, the fiscal burden severely strains available IHS resources.

One of the serious complications of diabetes among American Indians is end-stage renal disease (ESRD). In ESRD, kidney function is inadequate, and patients must receive either dialysis or kidney transplantation for survival. Data from the End-Stage Renal Disease Networks across the country show that approximately 40 percent of the American Indian and Alaska Native populations receiving dialysis or transplantation services in 1983 were known to have diabetes. Additional analysis of these data in 11 Western states (Alaska, Washington, Oregon, Idaho, Montana, California, Nevada, Arizona, New Mexico, Colorado, and Utah) indicates that the prevalence of ESRD among Indians in these states is approximately 525 per million, or 48 percent higher than for the overall U.S. population. In Arizona and New Mexico, the incidence of ESRD among American Indians is 123 percent higher than in the non-Indian population (table 3). With an average annual cost for dialysis of approximately $25,000 per patient, costs for diabetes-related dialysis in the Phoenix administrative area, 1 of 12 IHS administrative regions across the country, reached at least $2.6 million last year. These cost estimates reflect only one of the complications of diabetes in this population.

Table 3

END-STAGE RENAL DISEASE AMONG AMERICAN INDIANS, 1983

States	Indian Population*	ESRD Cases†	ESRD Crude Prevalence Rate (per million)
Alaska, Montana, Washington, Idaho, Oregon	213,909	59	276
California, Nevada	224,231	99	442
Colorado, Utah	38,881	19	489
Arizona, New Mexico	276,802	219	791
Total	753,823	396	525‡

* 1980 U.S. census data projected to 1983.
† 1983 HCFA ESRD Network data.
‡ Comparable ESRD rate for the total U.S. population is 354 per million.

THE MANDATES FOR DIABETES CONTROL IN AMERICAN INDIANS

In recognition of the severity of the diabetes problem, the Indian Health Service developed a plan for model diabetes care projects to be established at several existing IHS service units. This plan was

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presented to the National Commission on Diabetes during its deliberations in 1975-76. The Commission recognized that the proposed model projects could serve two important roles simultaneously: as a model for IHS initiatives throughout the Indian communities and as a model for low-income, medically underserved people in other areas of the United States. The Commission approved the concept and recommended that five model projects be developed in fiscal year 1978, with expansion to five additional sites in fiscal year 1980. The Commission also recommended that Congress appropriate additional funds to IHS for this program.

The Commission's recommendation was given high priority by the Board when it was established in 1977. The Board presented the proposed model program directly to Congress in early 1978. Recognizing the extent of the diabetes problem among Indian people, Congress endorsed this program and provided $925,000 in fiscal year 1979 to establish a small core program staff and a strong, technically competent group of health professionals at each of five sites. The five project sites were chosen by the Indian Health Service to represent different types of IHS facilities. The Claremore (Oklahoma) Indian Hospital is a multiservice referral facility located off reservation. The Fort Totten (North Dakota) Health Center is a reservation-based clinic without a hospital. The Sacaton (Arizona) program uses a small hospital with outlying clinics on the Pima reservation. The Winnebago (Nebraska) program uses both the reservation hospital and the tribally operated facility on the Omaha reservation. The Albuquerque (New Mexico) program serves urban Indians at the Albuquerque Indian Hospital, Pueblo Indians in village clinics, and a small band of Navajos. These five sites account for over 8,000 diabetes-related outpatient visits per year.

Multidisciplinary teams at each site have been organized to intensify preventive services for diabetic patients and to develop a comprehensive diabetes care plan that includes attention to related conditions such as hypertension, urinary tract infections, and foot care; routine screening for diabetic complications; nutrition counseling; and patient education. Record reviews show that considerable progress has been made at these five sites in delivering culturally acceptable diabetes care. It is expected that these programs, like others in several non-Indian facilities across the country, will be able to document decreased hospitalizations and morbidity, with a net reduction in total health care costs.

The model sites serve only about 10 percent of the IHS population; the other 90 percent is served by 50 additional service units. Transferring and implementing effective treatment strategies from the model sites to other service units has only begun. Requests for education, training, and assistance far exceed the available personnel and resources of the small core program staff.

INTERORGANIZATIONAL COOPERATION

Effective control of diabetes in American Indians goes far beyond the health clinic. To encourage a broader, cooperative, community approach to this effort, the Board has established an ad hoc American Indian Diabetes Coalition composed of individuals and organizations interested in this problem. This group has met on several occasions to discuss common goals, coordinate efforts, and share existing resources. Coalition members include representatives of the American Diabetes Association, American Indian-Alaskan Nursing Association, Association of American Indian Physicians, National Congress of American Indians, Indian Health Service, National Indian Health Board, National Tribal Chairmen's Association, Swanson Center for Nutrition, and several Board members. Priority activities of the coalition include:

- Increasing awareness, linkages, and activities of major groups responsible for or concerned with diabetes prevention and control among American Indians.
- Fostering a more active role by tribes, tribal agencies, and local groups in the prevention, care, and control of diabetes.
- Developing strategies that can reduce barriers to effective diabetes control programs within the IHS health care system.
- Strengthening the five model diabetes projects and encouraging expansion to additional service units.
- Adapting to the Indian situation available diabetes care information for dissemination to IHS and tribal health care personnel and to diabetic Indians and their families.
- Insuring adequate project documentation and evaluation. This is being facilitated by private foundation support for an evaluation feasibility and design study.

CURRENT FUNDING AND FUTURE RECOMMENDATIONS

The budget for this program remained at the 1979 level until fiscal year 1983, when Congress increased the appropriation to $1.4 million. These additional funds were used to remedy personnel needs that occurred after the program began; provide professional training and education to other IHS service

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units; respond to requests for technical assistance throughout IHS; and request proposals for innovative approaches to diabetes care in IHS service units without a model diabetes project.

Funds have not yet been provided for the projected five additional model projects needed in other geographic regions. Funds also are needed to extend the beneficial diabetes treatment and control practices of the model sites to other service units and to strengthen diabetes-related prevention and treatment services through professional education to insure clinical competence of health care providers. Additional technical assistance is needed for patient education, followup, and evaluation.

The Indian Health Service has recognized the magnitude of the diabetes problem and supports this initiative. However, IHS resources are already stretched thin, due in no small part to the growing cost of diabetic complications, such as kidney dialysis, cited above. IHS does not have the option of transferring resources from the treatment of chronic complications to the prevention of those complications. American Indians in need of dialysis, for example, must have the same access to such services as is provided for the general U.S. population. Therefore, IHS must receive the additional essential resources to support a priority program to prevent these diabetes-related complications. Such a prevention program must include patient education in daily self-care, screening for early signs of complications, and necessary ophthalmologic, podiatric, and prenatal services.

The Model Diabetes Care Program is the essential foundation for an IHS-wide diabetes control effort and has gained the necessary experience and information to warrant a broader outreach of its benefits. The initial outreach activities begun in fiscal year 1983 have identified both the need and the opportunity for an expanded program. The Board has carefully considered the needs of this program and recommends that the Congress increase the program's budget in fiscal year 1985 to $1.9 million. Additional funds are needed for the following purposes:

- **The model program should be expanded from five to seven sites:** The original plan proposed by the National Commission on Diabetes in 1976 provided for 10 model sites. The Board, in its first report to the Congress in 1978, recommended that only five sites be funded initially. We now recommend that model diabetes projects be established at two more clinics to permit expansion of this important program to additional geographic regions.

- **Additional outreach from the model program is essential:** This goal can be accomplished by providing modest startup funds to assist other health service units who wish to incorporate specific diabetes control approaches into their existing health care program.

- **Additional resources are needed within the existing model sites:** The addition of one staff member, such as a diabetes teaching nurse or other health professional, would permit several sites to greatly increase their effectiveness and expand their sphere of influence.

- **Additional equipment is needed:** Severe visual loss or blindness is a frequent complication of diabetes. Laser photocoagulation is an effective therapy to reduce the risk of this complication. Trained personnel experienced in the use of the laser are available in several sites serving large numbers of American Indians. However, IHS does not have laser equipment in the Southwest. Patients requiring this therapy are routinely sent to non-IHS facilities at a significant cost. Additional funds to purchase this equipment for selected medical centers would increase the quality and accessibility of care and result in a net savings in a short time.

In summary, the Board recommends that Congress increase the budget for the Model Diabetes Care Program of the Indian Health Service from $1.4 million to $1.9 million in fiscal year 1985 and that additional personnel and equipment necessary to carry out the program in each of the seven sites be provided without delay.

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8. NATIONAL STANDARDS FOR DIABETES PATIENT EDUCATION PROGRAMS

Patient education for self-management is an integral component of quality diabetes care. To be effective, however, the education provided must be up-to-date, of acceptable quality, and responsive to individual needs. The Board has observed inconsistencies for many years in the availability, accessibility, affordability, and quality of diabetes patients education programs throughout the country. The Board also is aware of the increasing number of studies that have documented significant reductions in hospitalization and related costs following carefully planned diabetes patient education programs.

In response to these studies, several third-party payors are beginning to reimburse outpatient education programs in selected localities (see pages 39 and 40 for examples). In each of these instances, a prerequisite for reimbursement has been the presence of clearly defined standards for the education program. The development of national standards would facilitate more rapid adoption of similar reimbursement policies throughout the country.

Against this backdrop, the Board undertook an initiative in April 1982 to develop national standards, associated support materials, and an implementation plan aimed at fostering the widespread availability of quality patient education programs. A Board-appointed steering committee, working collaboratively with experts from within and outside the diabetes community, convened five workgroups throughout 1982-83. These workgroups have completed the following tasks:

- Thorough review of existing standards and guidelines.
- Development of national standards that designate the elements of a quality diabetes patient education program.
- Widespread distribution of the national standards through publication in professional journals, presentation at professional meetings, and dissemination of over 10,000 individual copies.
- Preparation of support materials that assist a diabetes patient education program to meet the standards.
- Development of review criteria that establish specific parameters against which programs can measure themselves.
- Development of a national plan by which programs meeting the standards can be formally recognized.
- Initiation of a pilot study to test both the feasibility of implementing the standards and the usability of the support materials.

The pilot study is being conducted by a group of collaborating diabetes-related organizations under the auspices of the steering committee. It is scheduled for completion in October 1985. The results of the pilot study will form the basis for modification of the review criteria and adjustments in the recognition process prior to nationwide implementation.

The standards are already in demand. The intense interest they have generated reflects widespread awareness that the dramatic strides that have been made both in the treatment of diabetes and in preventive strategies have not been available to those who need to know. Further evidence of the favorable impact of the standards has been the development of two related conferences to be held in 1984. A conference in May, sponsored by the Humana Foundation, will focus on the current status and efficacy of diabetes patient education programs. Another conference in October, under the leadership of the American Diabetes Association, the Centers for Disease Control, and the Board, will examine the financing of quality diabetes care, including patient education and related reimbursement issues.

The formal announcement of the standards by the Board, reproduced below, presents the rationale for the initiative, a summary of the national implementation plan, a description of the standards, and a tabular presentation for easy reference.

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National Standards for Diabetes Patient Education Programs

National Diabetes Advisory Board November 1983

National standards for diabetes patient education programs have been endorsed by the National Diabetes Advisory Board. These standards were developed under the auspices of the Board and in collaboration with the American Association of Diabetes Educators, American Diabetes Association, Centers for Disease Control, Diabetes Research and Training Centers, International Diabetes Center (Minneapolis), Juvenile Diabetes Foundation, and National Diabetes Information Clearinghouse.

This statement presents the rationale for the standards and a plan for their implementation. It includes a summary and description of the standards and a tabular presentation for easy reference.

The Need for National Standards

Major strides have been made in the treatment of diabetes during the last decade as a result of biomedical research, technological advances, and improved application of currently available knowledge and resources. Dramatic increases in our knowledge of effective approaches to prevention of some of the complications of diabetes include better methods to assess and control blood glucose. It is now possible to limit the severity of some long-term effects of the disease and thus reduce its medical, social, and economic impact.

Several barriers, however, still preclude the widespread availability of preventive approaches in self-care. These barriers include lack of patient and provider knowledge about diabetes, inadequate reimbursement policies, and lack of coordination among key components of the health care system. One major impediment has been the lack of national standards to assure that the education provided to people with diabetes is of an acceptable quality and appropriate for the individual.

The National Diabetes Advisory Board, in collaboration with experts from within and outside the diabetes community, has developed national standards for diabetes patient education programs. These standards establish specific parameters against which programs can measure themselves. The standards are rigorous enough to be acceptable to the diabetes community, yet flexible enough to be practical for the primary care community. They are applicable in any health care setting. The Board encourages adoption of these standards by all diabetes patient education programs.

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National Plan for Implementation of the Standards

The National Diabetes Advisory Board (NDAB) is mandated by Congress to oversee the Long Range Plan to Combat Diabetes. In addition to its advisory role, the Board has come to serve as a forum through which the diabetes community can focus on common needs and problems and share in their solutions. Through a series of workgroups, the Board and cooperating organizations determined that the availability of the standards would be enhanced by a process to ensure their widespread application. They are therefore developing a national system of recognition for diabetes patient education programs that meet the standards. Recognition is a voluntary process through which programs meeting the standards are formally identified for a level of performance, integrity, and quality entitling them to the confidence of the community they serve. The process is flexible enough to apply to programs that conform to other standards, provided the other standards adhere to the national consensus standards or are modified to do so.

The standards and the recognition process will be pilot tested during 1984 and 1985. Pilot testing will be conducted under the auspices of a Board-appointed steering committee consisting of representatives of the diabetes-related organizations involved with the Board in the development of both the standards and the recognition process. These organizations include the American Association of Diabetes Educators, American Diabetes Association, Centers for Disease Control, Diabetes Research and Training Centers, International Diabetes Center (Minneapolis), Juvenile Diabetes Foundation, and National Diabetes Information Clearinghouse. The results of the pilot testing will form the basis for modifications in the standards and for any required adjustments in the recognition process prior to nationwide implementation. Support materials will be available to provide diabetes patient education programs with additional information on (1) how to meet the standards, (2) how to initiate or upgrade a program to meet them, and (3) how to apply for recognition.

Summary and Description of the Standards

Diabetes is a serious and common disease that is treated directly or indirectly in practically every health care facility in the nation, regardless of size or location.

In chronic diseases, especially diabetes, patients are required to assume a major share of responsibility for their own care. Only an informed and well-motivated person who has the support of the primary health care provider can carry out this responsibility effectively. Evidence is growing that inadequate patient knowledge results in multiple hospital admissions, excessive use of emergency rooms, unnecessary medication, and a high incidence of long-term complications of diabetes, all of which increase human suffering and escalate the costs of care. Studies testing patient education as the variable component of the treatment regimen have shown consistent reductions in these measures. Education for self-care is therefore recognized to be a fundamental component of quality treatment for the individual with diabetes.

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At the present time, both the quantity and quality of education offered to people with diabetes vary considerably in the United States. Experience in other fields has demonstrated the ability of uniform standards to improve the quality, effectiveness, and availability of programs. It is hoped that the implementation of national standards will result in increased access to this fundamental component of treatment by stimulating adequate reimbursement for diabetes patient education.

The diabetes patient education standards consist of 10 components that will enable an institution to establish a new program or modify an existing one. Each standard offers the flexibility required to tailor a patient education program to the type of diabetes, its duration, and the life-stage of the diabetic person. Many of the standards are overlapping, reflecting the interdependence among all components of an effective diabetes education program.

1. Needs Assessment. A successful program is the product of a flexible policy based upon the needs of the community it is intended to serve. Since the diabetes caseload varies from one institution to another, each institution should assess its own needs and match its resources to the needs of its caseload. The needs assessment should be performed initially to guide the management of the program and to form the basis for program planning. It should be a continuing process that will allow the program to adapt to changing service requirements. In addition to the needs of the program, the needs of the individual patient should be assessed to provide the basis for the instructional program offered to each patient. The person with diabetes is recognized to be an equal partner in all aspects of the educational process.

2. Planning. Planning is an essential component of a diabetes patient education program. The planning process should describe the program's goals and objectives, target audience, setting (inpatient, outpatient), patient-referral mechanisms, procedures, and evaluation methods. The planning process should be a cooperative effort involving people with diabetes as well as health professionals.

3. Program Management. Effective management is required to implement a patient education program. A variety of health care professionals is involved in the total care of people with diabetes. Clear lines of authority and efficient systems for communication should be established among everyone involved in the program. The ultimate responsibility for all aspects of program management should rest with one person designated as the program coordinator. In addition, an advisory committee should be established to assist the coordinator and other members of the program staff in setting policy and managing the program.

4. Communication and Coordination. Several levels of communication are essential to the effective coordination of the program. Physician leadership and participation are necessary to ensure the integration of patient education into the treatment regimen. A physician should be identified to serve as the liaison between the education program coordinator and the medical staff. In addition, the institution should maintain regular channels of communication with its staff and the community it serves to inform diabetes patients and their families about the availability of the program. All information on the patient's educational experience should be incorporated into the medical record.

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5. Patient Access to Teaching. It should be the policy of the institution to facilitate access to patient education for the target audience specified in the plan. This is promoted by a commitment to routinely inform both patients and staff about the availability and benefits of patient self-care programs. Diabetes patient education should be regularly and conveniently accessible, and the instructional program should be able to respond to patient-initiated requests for information. The program permits referral by health professionals, health care agencies, or individual patients. The instructional design encourages active patient participation.

6. Content/Curriculum. The individual patient's needs assessment provides the basis for the instructional program offered to each patient. The assessment should be documented and should include all relevant information regarding the patient's treatment, education, and support systems. Responsibility for various facets of the assessment can be divided among the instructional team members. Curriculum and instructional materials should be appropriate for the specified target audience, taking into consideration the type and duration of diabetes and the age and learning ability of the individual. Both curriculum and available community resources should be reviewed and updated periodically. The institution should provide the program with adequate space, personnel, budget, and materials.

7. Instructor. Qualified personnel are essential to the success of a diabetes patient education program. Each institution should be responsible for identifying and evaluating its instructors. Instructors should be skilled professionals with recent experience and training in both diabetes and educational principles. The number of instructors should be proportional to the caseload requirements. Instructors should be allotted sufficient time to complete the instructional program.

8. Followup. Followup services are important because diabetes requires a lifetime of proper care. The institution should provide followup services that include periodic reassessment of the patient's knowledge and skills and should offer supplementary educational services when warranted. Written communication between the program staff and the primary care physician is essential for ongoing identification of the patient's needs. This is especially appropriate in regard to referral for early diagnosis and treatment of the complications of diabetes. Referral to community resources may also provide ongoing support for long-term psychosocial needs and behavioral modification skills. If a patient changes care settings, the institution should request the patient's permission to send his/her records to the new health care setting.

9. Evaluation. The institution should review the educational program periodically to ascertain that it continues to meet the national standards. This review should be conducted by the advisory committee. The results of this review should be utilized in subsequent program planning and modification. An assessment of each patient's needs and progress should also be conducted at regular intervals.

10. Documentation. Program planning and evaluation should be documented to provide the basis for future program development and modification. All information about the patient's educational experience should be documented in the patient's medical records, as should communication among treatment and education professionals.

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National Standards for Diabetes Patient Education Programs

This table presents the standards in a form for easy reference. Standards applicable to the facility offering the program are designated "institution standards" and are separated from those applicable to the education program itself, which are designated "program standards."

	STANDARDS	
	Institution	Program
1. Needs Assessment	• The institution shall assess its diabetic caseload to determine the allocation of personnel and resources to serve the instructional needs of the caseload. • There shall be a reasonable match between caseload requirements and resources allocated.	• An individualized and documented ongoing assessment of needs shall be developed with the patient's participation. This shall include medical history, present health status, previous diabetes education, health services utilization, associated medical conditions or risk factors, diabetes knowledge, skills, attitudes, self-assessment, identification of support system, barriers to learning, and financial status. • The needs assessment shall be the basis for the education program delivered to each patient.
2. Planning	• The institution shall have a written policy that affirms patient education as an integral component of quality diabetes care.	• The participants in planning shall include health professionals involved in the care and education of persons with diabetes and persons with diabetes and their families. • The planning process shall define (in order): a) Program goals and objectives b) Target audience c) Program setting d) Patient access mechanisms e) Instructional methods f) Resource requirements g) Patient followup mechanisms h) Evaluation
3. Program Management	• A coordinator shall be designated and responsible for all aspects of the program. • The organizational relationships, lines of authority, staffing, and operational policies shall be defined. • A standing advisory committee with both medical and community/consumer representation shall be established.	• Not applicable.
4. Communication/ Coordination	• A physician shall be identified to serve as liaison between the program coordinator and the medical staff. • The institution shall regularly inform its staff and the patients (and potential patients) it serves of the availability of its diabetes patient education program.	• All information about the patient's educational experience shall be permanently incorporated into the patient's (medical) records maintained by the institution. • The role of each education team member shall be clearly defined, and the intercommunication between each shall be documented in the patient's record. • There shall be written evidence of coordination between different care settings.
5. Patient Access to Teaching	• The applicant institution shall have a policy to inform patients routinely about the benefits and availability of patient education.	• The program shall be regularly and conveniently available. • The program shall be responsive to patient-initiated requests for information and/or participation in the program's activities.

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COMPONENTS	STANDARDS	
	Institution	Program
6. Content/Curriculum	• The institution shall provide space, personnel, budget, and instructional materials adequate for the program. • Assessment of available community resources shall be performed periodically.	• The program shall be capable of offering information on each of the following content items as needed: a) General facts b) Psychological adjustment c) Family involvement d) Nutrition e) Exercise f) Medications g) Relationship between nutrition/exercise/medication h) Monitoring i) Hyperglycemia and hypoglycemia j) Illness k) Complications (prevent, treat, rehabilitate) l) Hygiene m) Benefits and responsibilities of care n) Use of health care systems o) Community resources • The institution shall specify the mechanism by which the curriculum shall be reviewed, approved, and updated.
7. Instructor	• The institution shall identify appropriate instructional personnel and ascertain their competence. • The numbers of personnel identified shall be suitable for the diabetic caseload within the institution. • Designation of time for identified instructors shall be appropriate to accomplish the necessary educational objectives.	• Instructors (health professionals and others) shall be part of a comprehensive care and education program. • Instructors shall have recent experience and training in diabetes and knowledge and skills in educational principles and their application.
8. Followup	• The institution shall transmit the educational record to other appropriate health care settings when a patient transfers his or her care responsibilities.	• The program shall provide followup services for those patients who wish to maintain continuity of education within the institution. These services shall include: a) Periodic reassessment of knowledge and skills b) Timely reeducation based on reassessment c) Communication with the primary care provider about the need for professional and nonprofessional services.
9. Evaluation	• The institution shall review periodically the performance of the instructional program and ascertain that it continues to meet national standards.	• The program shall conduct and record an individualized assessment of each patient's original needs and progress at regular intervals. • The program shall be reviewed in ongoing fashion for both process and outcome, and the results of this review shall be used in subsequent planning and program modification.
10. Documentation	• All aspects of the evaluation shall be recorded by the sponsoring institution and reviewed periodically to ascertain that national standards are being maintained.	• All aspects of the educational program offered to each patient shall be recorded in that patient's medical record as maintained by the institution.

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9. DIABETES-RELATED ACTIVITIES OF FEDERAL AGENCIES

The Federal Government is the major source of financial support for biomedical research and health care initiatives. Therefore, the success of the diabetes effort depends upon the quality and extent of Federal programs and the adequacy of Federal appropriations for this purpose. A summary of the major Federal diabetes-related activities is provided in this chapter.

NATIONAL INSTITUTES OF HEALTH

The National Institutes of Health is the major source of support for diabetes research and related manpower development. Most of the NIH Institutes and Divisions have specific areas of responsibility within the long-range diabetes plan.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases is the lead agency for federally supported diabetes research and is responsible for the planning, development, and implementation of a comprehensive national diabetes research program. The Institute also is the major source of support for training in diabetes-related research disciplines. NIADDK's manpower development program is described in chapter 5. Other special programs include the Diabetes-Endocrinology Research Centers, the Diabetes Research and Training Centers, and the Diabetes Control and Complications Trial, described in chapter 4. The Institute also supports the National Diabetes Information Clearinghouse and the National Diabetes Data Group.

National Diabetes Information Clearinghouse: The mission of the National Diabetes Information Clearinghouse (NDIC) is to facilitate an increase in knowledge and understanding about diabetes on the part of patients, health care providers, and the public through the effective dissemination of information. In its 5 years of operation, NDIC has identified, acquired, and written abstracts for over 3,000 diabetes education materials. Another 1,500 appropriate journal articles have been added to the database. These citations are published in topical annotated bibliographies and widely distributed.

The Clearinghouse publishes a bimonthly newsletter that informs the community of the latest developments in educational materials, publications, and related activities. It also responds to individual requests for information and materials. The Clearinghouse also has developed or assisted other organizations to develop priority information materials as needed.

National Diabetes Data Group: The National Diabetes Data Group (NDDG) is an advisory body of epidemiologists, medical specialists, data system experts, and representatives of several Federal and private agencies. NDDG was established in 1977 to define diabetes data needs in scientific and public health issues; foster the collection and analysis of such data; make reliable data available to users; measure the medical and socioeconomic impact of diabetes; and promote standards in data collection and reporting.

NDDG promotes research on epidemiologic and public health aspects of diabetes by serving as consultants to scientists regarding the suitability and feasibility of proposed epidemiologic research and by providing national data to researchers to contrast with their community-based epidemiologic data. The group currently is conducting a comprehensive compilation and assessment of data on diabetes to identify areas of needed new research in diabetes epidemiology.

National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) supports investigations in several areas that are fundamental to diabetes problems. For example, the metabolic effects and cardiovascular consequences of diabetes are major contributors to accelerated atherosclerosis, hypertension, coronary heart disease, peripheral vascular disease, and heart

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failure. In addition, NHLBI's epidemiologic investigations and clinical intervention trials on coronary heart disease include the evaluation of diabetes as one of several predisposing risk factors. Insulin-dependent diabetes patients also are being studied to evaluate the relationship of glucose control to the development of microvascular disease and to the classical risk factors that lead to macrovascular disease.

National Eye Institute

Diabetes is a major cause of blindness and vascular and circulatory abnormalities of the eye. The ocular complications of diabetes that eventually lead to blindness or visual impairment include diabetic retinopathy, diabetic cataract, and neovascular glaucoma. The National Eye Institute (NEI) supports fundamental research designed to elucidate the pathologic events associated with eye disorders; epidemiologic studies to identify risk factors associated with ocular complications; and clinical trials to evaluate the effectiveness of various forms of treatment. Several major clinical trials supported by NEI are described in chapter 4.

National Institute of Child Health and Human Development

Diabetes-related studies at the National Institute of Child Health and Human Development include research on diabetes in pregnancy, infants of diabetic mothers, nutrition, metabolism, obesity, and psychosocial issues in diabetes. Several diabetes initiatives, including clinical trials and Perinatal Emphasis Research Centers, are described in chapter 4.

National Institute of Allergy and Infectious Diseases

Diabetes-related research at the National Institute of Allergy and Infectious Diseases includes studies on infectious and immunogenetic factors that may induce diabetes and studies related to the causes, diagnosis, and treatment of diabetes. The Institute also supports developmental research on transplantation, including pancreas and pancreatic islet-cell transplantation, and on recombinant DNA technology and histocompatibility antigen systems.

National Institute of Neurological and Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke supports activities in a variety of neurobiological disciplines related to understanding the natural history of diabetes and its complications in the central and peripheral nervous system. Serious neurological complications involving both the sensory and motor functions of the peripheral and autonomic nervous systems may occur in up to 25 percent of all diabetic patients. The Institute's role in the Diabetes Control and Complications Trial and the activities of a peripheral neuropathy research center are described in chapter 4.

National Institute of Dental Research

The primary responsibility of the National Institute of Dental Research in relation to diabetes is to support research on the dental complications of the disease. The studies are concerned with the increased susceptibility of diabetic patients to periodontal diseases and the increased frequency of cleft palate in the offspring of diabetic mothers. In addition to these dental studies, the Institute's intramural program includes studies on human viruses as potential etiologic agents in certain types of diabetes.

National Institute on Aging

The National Institute on Aging is responsible for research related to the aging process and the diseases and other special problems of older people. Of particular concern are the interrelationships between diabetes and aging and their effects upon each other. The Institute's Gerontology Research Center is a particularly valuable resource for studies related to diabetes.

National Institute of General Medical Sciences

The National Institute of General Medical Sciences supports basic, noncategorical research that may have significance for diabetes and other categorical disease areas. Examples include fundamental genetic research, recombinant DNA technology, synthesis of new hypoglycemic agents, and the effects of diabetes on the pharmacology of drugs in general. The Institute's Medical-Scientist Training Program is especially important for future clinical research in all areas, including diabetes.

Division of Research Resources

The NIH Division of Research Resources (DRR) strives to meet the general research needs of the Na-

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tional Institutes of Health by increasing the availability of unique and essential resources. One DRR activity with direct application to diabetes research is the General Clinical Research Centers program, described in greater detail in chapter 4. DRR also supports resources in which animal models are developed and used in many diabetes-related projects, as well as the seven Regional Primate Research Centers, which provide specialized nonhuman primate resources for research on numerous diseases, including diabetes.

National Institute of Environmental Health Sciences

Research of the National Institute of Environmental Health Sciences related to diabetes consists of studies on the relationship between exposure to environmental agents and changes in pancreatic structure and function.

CENTERS FOR DISEASE CONTROL

The National Diabetes Control Program of the Centers for Disease Control seeks to reduce the social and economic costs of diabetes through the application of existing knowledge and traditional disease control techniques at the community level. Diabetes control demonstration projects are now under way in 20 states. A summary of project activities and accomplishments may be found in chapter 6. Several state projects have recently documented significant reduction in diabetes-related hospitalization and associated costs within their project areas.

HEALTH RESOURCES AND SERVICES ADMINISTRATION

Two major components of the Health Resources and Services Administration—the Indian Health Service and the Bureau of Health Care Delivery and Assistance—have responsibility for programs of importance to people with diabetes.

Indian Health Service: Diabetes mellitus has become a major health problem among American Indians, affecting over 40 percent of adults in some tribes. In recognition of this problem, Congress authorized the Model Diabetes Health Care Program to develop and evaluate effective and culturally acceptable methods to reduce the severity of the disease and its social and economic impact. A summary of the program is found in chapter 7.

Bureau of Health Care Delivery and Assistance: The Bureau seeks to assure the availability and accessibility of adequate health care to all citizens, particularly those who live in medically underserved rural and urban areas. Many persons with diabetes are provided care within the context of the Bureau's overall health service delivery efforts. For example, the Maternal and Child Health Program has a special opportunity to assist persons with diabetes while seeking to improve the quality of care to all expectant mothers.

ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION

The responsibility of the Alcohol, Drug Abuse, and Mental Health Administration with respect to diabetes resides predominantly within the National Institute of Mental Health. This Institute is responsible for Federal leadership in the area of psychosocial and behavioral problems. Much of the Institute's general research program is also applicable to diabetes, including research on the biochemistry of behavior; social and emotional development; psychopharmacology; biomedical and behavioral aspects of stress and illness; and psychological and sociological factors in coping, adaptation, and psychopathy.

NATIONAL CENTER FOR HEALTH STATISTICS

The National Center for Health Statistics conducts national studies to provide data about the medical, economic, and social impact of diabetes. This information is an important resource for the National Diabetes Data Group and other diabetes organizations concerned with research, health care services, and formulation of public policy related to diabetes.

VETERANS ADMINISTRATION

Medical care is a major statutory benefit for eligible veterans. The Veterans Administration (VA) conducts a comprehensive health care delivery program for its beneficiaries through medical centers and other facilities throughout the country. About 9 percent of all patients discharged from VA hospitals have a principal or associated diagnosis of diabetes. The VA also conducts extensive biomedical research and research training programs related to diabetes.

DEPARTMENT OF DEFENSE

The Department of Defense provides essential health care programs for the uniformed services and

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authorized beneficiaries. A variety of hospital and outpatient professional services for diabetes patient care are available. Each branch of the military service also supports biomedical research on a variety of subjects related to the health care needs of its members.

DIABETES MELLITUS INTERAGENCY COORDINATING COMMITTEE

The Diabetes Mellitus Interagency Coordinating Committee (DMICC) was established by Congress to improve the coordination of Federal research and health care programs related to diabetes. It provides both a forum for initiating agency interactions and a mechanism for tracking their progress. DMICC consists of representatives from 24 units of the Federal Government, all of which have some responsibility for diabetes-related activities.

An example of DMICC contributions to the Federal program is found in the "Conference on the Prevention and Management of Five Complications of Diabetes" sponsored by the DMICC in 1983. At this conference, the *Guide for Health Care Practitioners* was introduced to key representatives of Federal agencies that provide direct medical care services. Agency plans developed at the conference, reflecting each agency's unique needs and opportunities, are now being implemented. The Veterans Administration, the Department of Defense, and several agencies within the Health Resources and Services Administration, including the Indian Health Service, are conducting a variety of activities to disseminate and implement the treatment and prevention information contained in the *Guide*.

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10. NON-FEDERAL ACTIVITIES

The national effort to combat diabetes is much broader than the Federal programs described in this report. Individuals, families, communities, voluntary organizations, state and local governments, and industry all share the economic and social burdens of this disease. Each of these groups makes vital contributions to diabetes research, treatment, and prevention programs through their unique and essential activities. Without their leadership and participation, for example, the dissemination and implementation of research advances would not be possible. Private sector activities also complement the Federal research and manpower training programs in many critical areas.

The largest national voluntary organizations devoted entirely to diabetes are the American Diabetes Association (ADA) and the Juvenile Diabetes Foundation International (JDF). ADA supports research and development awards, feasibility grants, and research symposia. ADA also publishes *Diabetes Forecast*, an educational periodical for patients and their families; *Diabetes Care*, presenting information on clinical advances in this field; *Diabetes*, a journal devoted to scientific reports on diabetes and related research; and *Clinical Diabetes*, a bimonthly publication for primary care physicians.

The major goal of the Juvenile Diabetes Foundation is the direct support of diabetes research in its broadest sense. JDF awards research grants, research fellowships, and clinical investigatorships. It also has an active program to organize and fund worldwide research symposia. In addition, JDF provides parent and peer counseling, patient education, and informational brochures. In 1980, the National Diabetes Research Interchange was established as a program of JDF to advance the procurement, preservation, and distribution of human tissue and organs for research. This program, now independent of JDF, has been successful in establishing a network to retrieve human tissue that otherwise would have been wasted.

Several examples of private industry's contributions to diabetes research and treatment are included in this report. The production of human insulin by recombinant DNA technology now assures adequate supplies of this essential hormone. The development of highly purified insulin preparations is valuable to some persons with diabetes who experience allergic reactions to conventional insulin. Other examples of private industry's contributions include the development of insulin infusion and self blood glucose monitoring devices, participation in clinical trials, development of new drugs for the treatment of diabetes, support for research symposia and postgraduate professional courses, development of patient education materials, and direct support of basic research in selected areas.

In many instances, initial research in these areas was supported by various NIH programs. However, as scientific knowledge progressively advances toward commercial or community application, the focus of support has shifted from the Federal to the state, local, and private sectors. These are but a few of many examples that illustrate the interrelationships between Federal and non-Federal activities.

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